Scientists react to republished Séralini GMO maize rat study

Scientists around the world react as a controversial animal study on genetically modified (GM) corn and glyphosate-based herbicide that had been published and then retracted has been republished in expanded form in another academic journal.

The study, “Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize” by a group of French scientists led by Gilles-Eric Séralini, claims that a Monsanto herbicide-tolerant GM corn and RoundUp, Monsanto’s brand name for the herbicide, caused severe diseases and tumor growths in rats. It was republished today in the open-access journal Environmental Sciences Europe (SpringerOpen).

The study was originally published in *Food and Chemical Toxicology* (Elsevier) in September 2012. It met strong criticism from the scientific community almost immediately, with concerns ranging from the validity of the findings to the proper use of animals in the study. In November 2013, *Food and Chemical Toxicology* retracted the study.

In the previous publication, Séralini and colleagues faced immense pressure from the scientific community to release the raw data collected for the study. They did not do so then, but in the study’s current republication and expanded revision, the raw data has been made available.

Here, the GLP posts a collection of the responses from scientists worldwide to the study and raw data release. We will post more reactions—critical and in support of the findings–as they become available.

David Spiegelhalter, Winton professor of the public understanding of risk at the University of Cambridge, said:

> The article still does not appear to have had proper statistical refereeing, and the methods and reporting are obscure. The claimed effects show no dose-response, and so the conclusions rest entirely on a comparison with ten control rats of each sex. This is inadequate.
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> The study needs replicating by a truly independent laboratory using appropriate sample sizes. I agree with the authors that this whole area would benefit from greater transparency of data and improved experimental and statistical methods.

Joe N. Perry, quantitative ecologist and visiting professor of biometry at the University of Greenwich, said:

> This paper appears to be based on the same data as Séralini’s previous 2012 paper, with no real new information and only minor rephrasing and a few new references. Therefore, I doubt whether my conclusions would differ from those of the vast majority of independent members of the scientific community, who concluded in 2012 that there was insufficient evidence to

justify the claims of CRIIGEN and Giles-Eric Séralini. However, I do welcome Séralini's promise to publish his raw data and my hope is that all organisations involved in GM risk assessment will, wherever possible in the future, publish in full their raw data in the spirit of full transparency and openness.

Marcel Kuntz, biologist, director of research at Centre National de la Recherche Scientifique (CNRS, France) and professor at University of Grenoble-Alpes, said:

The authors reach essentially the same conclusions that were already refuted and they don't take into account the fundamental criticisms addressed to them.

Looking specifically at the tumors: The breed of rats used is subject to spontaneous tumor development. To identify a statistically reliable increase in tumors in a group of rats requires a large number of individuals. This re-publication is still deficient on this point.

These tumors were the most spectacular element of the media operation conducted by the authors. It should be noted that they showed photographs of three rats: a rat that used the GMO NK603, another that drank Roundup and a third absorbed both. Unlike the most basic scientific approach, no control rats (which didn't eat GMO or drink herbicide) were shown. These control rats are still not shown in the re-publication.

Disclosure statement for Marcel Kuntz:

My only income comes from my employers mentioned above (and marginally the copyright of my books). I have no current contract with a private company, or as an individual, nor to my laboratory. My current scientific work is basic research, unrelated to the marketing of a variety of plant (GM or not). I don't hold any patents, nor collect, nor received income as an inventor of a patent held by others. I do not identify any change in this situation in the foreseeable future.

Tom Sanders, professor of nutrition and dietetics at the King's College London School of Medicine, said:

Republishing data that was faulty in the first place in study design and analysis does not provide redemption. Furthermore, it is now possible to publish almost anything in Open Access journals!

Séralini did not follow conventional methods for assessing animal toxicity and made most ofthe measurements at the end of life. When a very large number of measurements are made, statistically significant differences will occur play of chance.

The figures of an animal with a large tumour serve no scientific purpose. There are numerous omissions of probabilities which could lead the less critical reader to infer differences that are not statistically significant.

Bruce Chassy, professor emeritus of food safety and nutritional sciences from the Department of Food Science and Nutrition at the University of Illinois, Urbana-Champaign, said:

The original Séralini paper was rejected for many reasons. Perhaps the most important of these was that the design of the study and the described methods for data collection were fatally flawed in a number of ways. No amount of rewriting or excuses for faults can make the data whole again. When the data are faulty, the experiment must be repeated with proper design and methods.

Food and Chemical Toxicology and Elsevier have acted poorly throughout this affair. It is difficult for experts to understand why Food and Chemical Toxicology published the paper since it is exceedingly challenging to find an expert peer-reviewer who cannot find numerous flaws in the paper. The journal then consumed more than a year to retract the paper.

Among the several reasons for retraction that Food and Chemical Toxicology failed to cite was the unethical use of animals in experiments which the Committee on Publication Ethics states is a reason for retraction.

Séralini now states that the research was not a cancer study. If that is true, then there was no reason not to euthanize animals when tumors were first detectable. There was nothing to gain or learn. This is unethical treatment of animals.

Christopher Preston, lecturer in the School of Agriculture, Food and Wine at the University of Adelaide said:

The sample sizes are too small, and there are too many treatments and not enough controls. The wrong breed of rat is used. As it is prone to high numbers of tumours, there is going to be a lot of noise and not enough statistical power. There is no dose response, i.e. they were just

measuring noise. There are ethical issues with the treatment of the rats.

My guess at why Séralini has pulled out of the (EU) repeat is because other scientists want to do the trial correctly. Séralini knows he can find something to spin if it is done his way because the likelihood of one of the 9 treatments being different to the control is quite high.

Wayne Parrot, professor of crop science at the University of Georgia Institute of Plant Breeding, Genetics & Genomics, and Department of Crop & Soil Sciences, said:

Séralini to this day fails to say what about modification would cause cancer. It is as if a magical carcinogenic aura was imposed on the GMO. Looking at rat studies with a real carcinogen (Aristolochia herbs), the onset of tumors in a dose-dependent matter is rapid, and reaches 100% by 16 weeks. Séralini is not even in the ballpark.

Andrew Bartholomaeus, adjunct professor of toxicology and pharmacy at the School of Pharmacy, University of Canberra, and Therapeutic Research Unit, School of Medicine, University of Queensland said:

This paper is largely a re-publication of the original article published and subsequently retracted by Food & Chemical Toxicology due to concerns around the scientific quality of the study and its interpretation, with some amendments that qualitatively address some of the criticisms of the original.

The science of the original publication was carefully assessed by food regulatory agencies, including the European Food Safety Agency (EFSA) and Food Standards Australia NZ (FSANZ). EFSA concluded that the design analysis and reporting is of insufficient scientific quality to be relevant in the safety assessment process.

The damming criticisms of the European Society of Toxicologic Pathology (ESTP), the peak body for experts in the diagnosis and interpretation of animal pathology findings, remain most relevant. ESTP concluded that the interpretation of findings included such basic errors that they would “be considered as a disqualifying mistake at an examination for pathologists” and stated they were “shocked by the whole body photographs of animals bearing very large tumors… which should have been euthanized….much earlier…….as the authors only illustrate that Sprague Dawley rats develop mammary tumors..(which are) common background lesions” in this strain of animal.

From a toxicological or food safety perspective the conclusions ANZ and international food regulatory agencies and peak scientific bodies suggest that the paper has insufficient scientific merit even to be considered controversial or provocative and will likely to be essentially irrelevant to the mainstream scientific community. None of the changes alter thesefundamental criticisms.

In short the paper is likely to raise little more than a yawn amongst the mainstream toxicology and food regulatory communities. As an exercise in media management however the republication and associated commentary and media management such as the embargoes and limited access, reflects a masterful flair for publicity generation.

Unfortunately such studies, and the associated publicity, may lead to more serious public health consequences than those purported to be found in the studies themselves, as illustrated by the vandalism of field trials of Golden Rice in the Philippines, a crop being developed to alleviate the chronic disease and premature death of some of the worlds most desperate and disadvantaged children, suffering chronic vitamin A deficiency.

Declaration of interests for Andrew Bartholomaeus:

I have no direct financial interest in commercial biotechnology activities, either currently or at any time in the past. Before retiring I was the Branch head for the Risk assessment Branch of FSANZ, and prior to that the chief toxicologist for the prescription medicines branch of the TGA. I currently consult, primarily to Government, on science policy and practice in regulation and perform human health risk assessments for various areas of government. I have also collaborated with ILSI (free of charge) to deliver workshops on biotechnology risk assessment for regulators around the world and to publish papers on this topic.

Ian Musgrave, senior lecturer in the Faculty of Medicine, School of Medicine Sciences, within the Discipline of Pharmacology at the University of Adelaide, said:

A French research study that claimed that rats fed a diet which contained a Roundup-tolerant genetically modified maize died more frequently and earlier over the two year study than control groups was retracted last year after widespread criticism of its methodology and interpretation. It has now been republished. However, the major flaws in this study still remain.

1) The wrong controls were used – there should have been a non-GMO control for each level of GMO corn (i.e. there should have been an 11 per cent control for the 11 per cent GMO corn, a 22 per cent control for the 22 per cent GMO corn and 33 per cent standard corn for the 33 per cent GMO corn. As energy content, carbohydrate load and other components of the corn may affect tumour formation, this is a fundamental flaw which invalidates any conclusions.

2) There is no dose response. For a substance to be an attributable cause of cancer, being

exposed to more of the substance should result in more cases of cancer this just does not happen in this study.

3) Furthermore, there is no consistent response to any of the measured outcomes that would even hint at a real adverse effect. The GMO corn had no effect on the number of tumours – Roundup even decreased the number of tumours in male rats, as did the combination of roundup and GMO corn in male rats (there was no consistent effect in female rats). High levels of GMO corn and high levels of roundup both reduced spontaneous mortality and pushed back the onset of death in male rats.

This shows that all we are seeing in these results is due to random variation in a poorly controlled experiment. It does not show that GMO corn, or roundup, even at concentrations that no human would ever be exposed to through diet, have no effect on cancer or mortality.

Thomas Lumley, professor from the Department of Statistics, University of Auckland, said:

I do not think the republication of the Séralini paper and the responses to critics answer any of the statistical concerns I had with the original paper. The main point of the response over sample size is to argue that some standard toxicological studies also use small sample sizes, which may be true but would not be relevant.

Although I do not find it convincing, I am pleased that the study is being republished. While I think it would have been reasonable to reject the paper initially, I was uncomfortable with a retraction that was not based on any new information or any accusation of wrongdoing, and said so at the time.

Since the responses to critics claim that much of the opposition is a smear campaign by people funded by Monsanto and the GM crop industry, I think it is appropriate to point out that I have never received funding from Monsanto or any company involved in GM crop technology.

Robert Wager, technician and faculty member in the Biology Department at Vancouver Island University, said:

There are two main issues with the data I think need explanation by Séralini. First, the basic rule of toxicology is the dose makes the poison. Everything can be toxic if the dose is high enough. Therefore all proper toxicology studies show dose response curves (the higher the dose, the greater the effect). None of the data in the Séralini paper show dose response curves.

The second point and probably more important point is the use of inappropriate strain of rats. Sprague-Dawley is a strain of rat that spontaneously generates tumors. For this reason they are extensively used in cancer research. One of the main criticisms of the original 2012 paper

was the omission of the control rat data and photos. The re-release again does not show the control rats.

It is very clear that review of the science literature show the conclusions of Séralini et al. are not supported by the vast majority of publications in this area.

Disclosure statement for Robert Wager

I have no financial connection with any biotech company. I have never received any personal pay from any biotech company, nor does my institute receive/administer and grants from biotech companies. I have serious difference of opinion on GMO's with Séralini et al. but have no connection to him or his institute. I am an academic who hates the impact pseudo-science is having on public policy and that is my only motivation.

Alan McHughen, plant biotechnologist and geneticist at the College of Natural and Agricultural Sciences, University of California, Riverside, said:

The number of rats used was too small to detect a meaningful difference in treatments. In this 'new' study, the number of rats remains the same, too small to yield meaningful results. To illustrate for those not familiar, it's as if Séralini tossed a coin two times, and the coin came up 'heads' both times. With this result, Séralini is trying to convince us that he has a magic coin that only comes up 'heads'.

The strain of rats used (Sprague-Dawley) was inappropriate for this type of two-year long study, as these rats have a natural predisposition to form tumors, regardless of the treatment. Séralini has not and can not justify this fatal error in experimental design

Séralini now asserts that he follows all European ethical guidelines for animal care. But he still shows rats with massive tumors, and the European ethical standards requires rats be euthanized when tumors reach 4 mm diameter. Clearly the rats in the photos have tumors larger than 4 mm, about the size of a small pea.

There's no dose response. In toxicity or carcinogenicity studies, increasing the dose of an actual toxin or carcinogen leads to greater effect. But Séralini's data do not show such dose effects, and Séralini still does not properly explain why.

In short, the 'new' paper will have the same impact as the original, retracted paper, because the original data were useless, and there is no new data. The methodology was faulty then, and, as there is no new methodology, it remains faulty now.

When the results of an experiment fail to reflect what we observe in the real world, the scientist knows the experimental design or interpretation must be wrong and tries to correct it. But Séralini insists his experiments and interpretations are fine; it's reality that's wrong.

Disclosure statement for Alan McHughen:

I am happy to advise that I am a public sector academic scientist serving the public interest, and as such, my research program is funded entirely from public sources; I do not accept private funds. As a result, I have no research connection to either Mr Séralini (or his coauthors), or CRIIGEN, or Monsanto.

Cami Ryan, professional affiliate with the Department of Bioresource Policy, Business and Economics at the College of Agriculture and Bioresources, University of Saskatchewan, said:

First, and most importantly, this is the same poorly designed scientific study that has been widely discredited by health and food safety agencies all over the world when it was published in 2012 (and subsequently retracted in 2013) by Food and Chemical Toxicology. Sample sizes and controls are still a problem (there are well-articulated OECD guidelines on this) and there are several holes in terms of interpretation of data.

If Séralini's goal here was the pursuit of good, quality science, he would have accepted the original retraction, paid mind to the broader criticisms that he received from subject-matter scientific experts and organizations and executed a new study (using an appropriate methodology) before attempting to publish again. Quality science is published in quality journals. If Séralini was really onto something here, it most certainly would have been taken up by more reputable academic journals such as Nature or Science.

Disclosure statement from Cami Ryan:

My current work is funded through various entities including not-for-profit grower groups and organizations as well as Genome Canada's Genome Prairie/GELS program. No conflict.

Peter Dearden, associate professor and director of Genetics Otago, Laboratory for Evolution and Development at the University of Otago, said:

The republication of the Séralini study raises a number of important issues to do with the scientific process. It must be noted that the paper being published is identical to the first one, which was initially attacked on methodological bases.

The paper is being republished because the authors feel it was unfairly retracted from Food and Chemical Toxicology. I think that the problem here is the controversial nature of theoriginal paper.

This was a publication that gave some interesting results, but that needed to be replicated with larger numbers of rats in the experiment and, perhaps, a more statistically robust analysis. The paper was, in my mind, inconclusive, but pointed a direction in which future research could go.

After much public discussion the paper was withdrawn by the journal against the wishes of the authors. This is unusual. Even more unusual is the notice of retraction that states that the study was inconclusive, but there was no flaw or fraud in the original paper. Inconclusive data is no reason to retract a peer-reviewed and published paper.

The republication of this paper, and the rebuttals presented, have not changed my opinion. I am not convinced that the original paper indicates any danger of genetically modified food. I do think, however, that this research needs to be continued.

I am also convinced that retracting the original paper in this unusual way has not served the scientific process well. All good science is a debate, and one that should be held publically in published journals. Only through open publication, replication and exchange of scientific data can we use science effectively.

Controversial studies should not be buried because of public argument. They should be investigated, repeated, and new data published to either disprove or support the original findings. Only then do we get a clear and robust argument.

Jack Heinemann, professor of molecular biology and genetics at the University of Canterbury New Zealand, said:

The first publication of these results revealed some of the viciousness that can be unleashed on researchers presenting uncomfortable findings. I applaud Environmental Sciences Europe for submitting the work to yet another round of rigorous blind peer review and then bravely standing by the process and the recommendations of its reviewers, especially after witnessing the events surrounding the first publication.

This study has arguably prevailed through the most comprehensive and independent review process to which any scientific study on GMOs has ever been subjected.

The work provides important new knowledge that must be taken into account by the community that evaluates and reports upon the risks of genetically modified organisms, indeed upon all sources of pesticide in our food and feed chains. In time these findings must be verified by repetition or challenged by superior experimentation. In my view, nothing constructive for risk assessment or promotion of GM biotechnology has been achieved by

attempting to expunge these data from the public record.

Michael Antoniou, head of nuclear biology group at King's College London, said:

> Few studies would survive such intensive scrutiny by fellow scientists. The republication of the study after three expert reviews is a testament to its rigour, as well as to the integrity of the researchers.
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> If anyone still doubts the quality of this study, they should simply read the republished paper. The science speaks for itself.
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> If even then they refuse to accept the results, they should launch their own research study on these two toxic products that have now been in the human food and animal feed chain for many years.

Responses collected through the Science Media Centre and Sustainable Pulse.