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PERSPECTIVE

Plurality of opinion, scientific discourse and pseudoscience: an in depth analysis of the Séralini et al. study claiming that Roundup™ Ready corn or the herbicide Roundup™ cause cancer in rats

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Abstract A recent paper published in the journal *Food and Chemical Toxicology* presents the results of a long-term toxicity study related to a widely-used commercial herbicide (Roundup™) and a Roundup-tolerant genetically modified variety of maize, concluding that both the herbicide and the maize varieties are toxic. Here we discuss the many errors and inaccuracies in the published article resulting in highly misleading conclusions, whose publication in the scientific literature and in the wider media has caused damage to the credibility of science and researchers in the field. We and many others have criticized the study, and in particular the manner in which the experiments were planned, implemented, analyzed, interpreted and communicated. The study appeared to sweep aside all known benchmarks of scientific good practice and, more importantly, to ignore the minimal standards of scientific and ethical conduct in particular concerning the humane treatment of experimental animals.

Keywords Safety assessment · GM crops · Toxicity · GM maize

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Introduction

It started with a press conference in which journalists agreed not to engage in fact-checking in return for a preview of new research indicating that both a widely-used herbicide and a genetically modified variety of maize resistant to that herbicide caused high levels of tumors in rats (Butler 2012). Within hours, the news had been blogged and tweeted more than 1.5 million times. Lurid photos of tumor-ridden rats appeared on websites and in newspapers around the world, while larger-than-life images of the rats were broadcast across the USA on the popular television show Dr. Oz. Activists destroyed a GM soybean consignment at the port of Lorient, France, in order to denounce the presence in the food chain of a product they considered to be toxic (Vargas 2012). The Russian Federation and Kazakhstan banned imports of the maize variety used in the study, Peru imposed a 10-year moratorium on GM crops (Bernhardt 2012) and Kenya banned all imports of GM food (Owino 2012).

The corresponding original research article was published in the journal *Food and Chemical Toxicology* (Séralini et al. 2012). The European Food Safety Authority (EFSA) and its counterparts in Australia, New Zealand and Canada were quick to criticize the study and its outcomes, and a joint statement condemning the article was released by six French academies (Supplementary References 1, EFSA 2012). The tide of criticism was joined by the competent national authorities in Belgium, Brazil, Romania, France, the Netherlands, Germany and Denmark, as well as numerous prominent scientists attacking the study on ethical, methodological and statistical grounds (Supplementary References 2). At the same time, some long-term opponents of GM crops heralded the study as proof that current risk-assessment practices are deficient and unsuitable (Supplementary References 3).

In this article, we discuss the many shortcomings of the Séralini paper and dissect its erroneous conclusions. We also discuss the consequences of permitting such poorly-executed research to be reported in the media without challenge, and conclude that the editor of *Food and Chemical Toxicology* should have retracted the paper based on its clearly flawed data, its breaches of ethical standards, and the strong evidence for scientific misconduct and abuse of the peer-review process. We welcome diverse interpretations of scientific data as long as these are supported by experimental evidence and data analysis, because this is necessary for scientific progress. However, we are highly critical of the flawed science in the Séralini paper, and of the irresponsible media reporting surrounding it, which violates internationally accepted professional ethical standards of journalism.

One of the cornerstones of science is communication within the scientific community and with the public. The Séralini paper is a regrettable example of failures at multiple levels during the execution and communication of research, including the inability to formulate a valid hypothesis, implement sound and unbiased experiments, analyze the results properly, report the experimental outcomes objectively, allow other researchers access to raw data, and separate accurate observations and conclusions from artifacts. With specific regard to the reported animal studies, there was also an abject failure to treat the experimental animals in a humane manner, within the standards of the national and international regulatory authorities.

The aim of this article is to expose these failures and discuss their potential impact while retaining a position that is entirely consistent with the coexistence of diverging interpretations of data, as long as these conform to minimum standards of professional scientific and ethical conduct.

Plurality of opinion and democracy in science

The Séralini paper, and its associated media fanfare, was a transparent attempt to discredit regulatory agencies around the world, and to get the public to insist on different standards of regulation for GM crops (Entine 2012). The authors asked the journal to delay publication while they organized the media event, and the journal article was accompanied by a video entitled *Tous cobayes?* (Are we all guinea pigs?) (http://www.youtube.com/watch?v=AoI_LiWhWq0) and the publication of a book on the same topic, which collectively helped ensure maximum impact.

These events raise issues about the role of plurality of opinion and democracy in science and its regulation, and the link between science and public understanding. Carl Sagan once said: "We have designed our civilization based on science and technology, and at the same time arranged things so that almost no-one understands anything at all about science and technology—this is a

clear prescription for disaster." The Séralini paper provides a clear example of how disaster could arise from science policy based on the plurality of opinion forged by poor science rather than rigorous scientific data. Regulatory bodies exist to provide objective assessments. They comprise experts on the topic with the authority to establish regulations that ensure society benefits from scientific discoveries, rather than coming to harm. Therefore plurality of opinion not supported by relevant data and propelled by democracy in science undermines the very institutions put in place to ensure the proper use of science and technology for the benefit of society (Entine 2012).

Transparency and open discussions are good for science

Early scientists wrote letters to each other announcing their results. Although the goal was to announce advances while establishing priority and therefore achieve prominence and economic gain, the open publication of such letters gave other scientists the opportunity to verify data and to build on previous experiments, which is the foundation of scientific and technological development in society today. Publication also provided transparency and allowed open discussion, so that poor science could be criticized and discarded. As modern science evolved into a formal discipline, this tradition of open discussion led to the development of peer review as the requirement before publication in scientific journals. The *Philosophical Transactions of the Royal Society* were the first to begin reviewing articles prior to publication, alerting authors to issues that might affect the interpretation of their results. The practice spread to other journals and became the accepted standard, so that credibility in science could only be established by publishing experiments that could be repeated by others and subjected to scrutiny. Credibility in science also depends on self-policing, along with procedures to ensure allegations of misconduct are properly investigated and if true, that proper actions are taken to correct the misconduct (Office of Science and Technology Policy 2000).

It is therefore a disturbing trend that when the science is indefensible, the tactic has become one of questioning the right of other scientists to critique questionable results. Scientists who have questioned Séralini's flawed results have been automatically accused of corporate corruption or of making attacks on academic freedom (Supplementary References 4).

Principal claims of the Séralini article

The stated objectives were to assess the potential toxicity of a glyphosate herbicide-resistant GM maize variety (with and without the application of herbicide) and also independently the herbicide itself on Sprague-Dawley rats over a period of 2 years (Séralini et al. 2012). We briefly reproduce the author's claims in this section for further discussion.

The methodology was described as follows: 200 Sprague-Dawley rats (100 males and 100 females, divided into ten treatment groups) were fed on glyphosate-tolerant transgenic maize line NK603, expressing the enolpyruvylshikimate-3-phosphase synthase (EPSPS) gene from *Agrobacterium tumefaciens* strain CP4. Three groups of rats were fed different doses of GM maize (11, 22 and 33 % of the diet) treated with the glyphosate-based herbicide Roundup, three groups were fed with the same doses of GM maize without prior treatment with herbicide, and three groups were fed a controlled diet but different doses of Roundup were added to the drinking water. A final group was fed on 33 % non-GM maize with no herbicide exposure.

The authors stated (although they did not provide data) that quantitative PCR was used to verify the presence of the EPSPS transgene in the GM maize diets, and that compositional analysis confirmed substantial equivalence between the GM and non-GM diets except the presence of the transgene. They also claimed there were no contaminating pesticides over standard limits (data not shown).

The experiments as reported focused on food and water consumption, body weight, behavior, appearance, tumor palpation and clinical observations carried out twice each week. Blood and urine samples were collected before, during and at the end of the experiment (in total 11 samples) to study hematology, coagulation and biochemistry. At the end of the experiment, surviving animals were sacrificed and tumors (as well as 34 organs) were dissected and either weighed or processed for anatomopathology and transmission electron microscopy. Statistical analysis was based on multivariate analysis to model, analyze

and interpret blood parameters across the treatment groups (Eriksson et al. 2006a, b). Finally, they used orthogonal partial least squares discriminant analysis (OPLS-DA) to find parameters that diverged within groups thus obtaining outcomes significant at 99 % confidence levels (Weljie et al. 2011; Wiklund et al. 2008).

The authors reported that 30 % of males (3/10) and 20 % of females (2/10) in the control group died spontaneously, whereas more than 50 % of the males and 70 % of the females died when fed on GM maize without herbicide. This comprised 5/10 males fed on 11 % GM maize, 1/10 males fed on 22 % GM maize, 1/10 males fed on 33 % GM maize, 2/10 females fed on 11 % GM maize, 7/10 females fed on 22 % GM maize and 4/10 females fed on 33 % GM maize (Table 1). There was no relationship between mortality rate and the dose e.g. the highest mortality in males occurred in the 11 % GM maize group and the high mortality in females occurred in the 22 % GM maize group. Indeed, if the two male groups fed on GM maize are combined, the incidence of early mortality (7/30 or 23 %) is actually lower than that of the control group. Similarly inconsistent results were obtained in the groups fed GM maize plus Roundup (e.g. 5/10 males fed on 22 % GM maize plus Roundup vs 3/10 males fed on 33 % GM maize plus Roundup; 7/10 females fed on 22 % GM maize plus Roundup vs 4/10 females fed on 33 % GM maize plus Roundup).

The authors reported that the prevailing cause of death was large mammary tumors in females and various tumors in males. Females exposed to Roundup in the drinking water also had a shorter lifespan than females in the control group (Table 2). They stated that 95 % of the palpable tumors were non-regressive, including adenomas, fibroadenomas and carcinomas, and that although the tumors were not dose-dependent they increased in number and size as the animals grew older as evidenced by selected images.

Large tumors were reported to be five times more frequent in females than males at the end of the experiment, and 93 % of them were breast tumors which caused breathing difficulties, intestinal obstructions and hemorrhages. The pituitary glands in female rats were twice as likely to be affected as those in males, whereas the most affected organs in males were the liver and kidneys (nephropathy was twice as prevalent at the highest dose of herbicide compared to the lowest dose). The authors also reported that females fed on GM maize experienced hormonal imbalance which was linked to pituitary dysfunction and the occurrence of mammary tumors. They concluded that low levels of Roundup herbicide (concentrations below official safety thresholds) have a significant impact on kidney, liver and breast tissues, reflecting the disruption of maize metabolic pathways caused by transgene expression resulting in the accumulation of toxic compounds. The authors recommended that the toxicity of GM crops and pesticides should be monitored by carrying out additional long-term assessments.

Table 1 Mortality (by euthanasia or spontaneous mortality) in different groups of 10 rats, separated by the amount of maize in the diet (from Séralini et al. 2012)

Diet	Dose (%)	Number of dead males (n = 10)	Number of dead females (n = 10)
Conventional maize	33	3	2
GM maize	11	5	3
	22	1	7
	33	1	4
GM maize plus Roundup™	11	4	4
	22	5	7
	33	3	4

Critical deficiencies in the Séralini article

The Séralini article claims to address the toxicity of herbicide-tolerant GM maize in the diet, with or

Table 2 Mortality (by euthanasia or spontaneous mortality) in different groups of 10 rats separated by the amount of Roundup™ in the drinking water A: B: C: 0.5 % (from Séralini et al. 2012)

Group	Dose	Number of dead males (n = 10)	Number of dead females (n = 10)
No herbicide	0	3	2
Herbicide in drinking water	1.1×10^{-8} %	3	5
	0.09 %	4	5
	0.5 %	1	4

without Roundup herbicide, and of Roundup alone when administered in drinking water at levels equivalent to 50 ng/L, 400 and 2,250 mg/L of glyphosate. Since the water consumption was not measured it is not possible to calculate the real exposure to glyphosate from these concentrations. The authors attempted to justify the use of commercial formulations rather than the pure active ingredient on the tenuous basis that environmental exposure is to the whole product. The weakness of this argument is apparent from the differing behavior of formulations and their ingredients in terms of environmental stability, mobility in ground water, adsorption to soil, resistance to water-treatment protocols and the complex compositional nature of any body of water intended for human or agricultural use. The design, implementation and interpretation of this research were flawed in so many ways and on so many levels that a comprehensive critique could easily exceed the space available here. Indeed, an avalanche of criticism has erupted from the scientific community and regulatory agencies in response to the paper (Supplementary References 1 and 2). The most serious flaws are summarized in Table 3.

Poor study design

The key flaw in the paper is the poor study design, which is based on the discredited hypothesis that inserting a gene into the genome of a crop species is inherently more likely to produce unintended, unexpected and hazardous characteristics than would be the case using conventional breeding. Despite the commercialization of hundreds of GM crops over the last 20 years, there is no evidence that any novel toxin has been produced de novo by gene insertion (Snell et al. 2012). Whole food studies are inherently weak, with the major limitations summarized by Elias (1980) in a discussion relating to the toxicity of irradiated food:

> "…the impossibility of physically or chemically identifying what was being tested; the inability to incorporate sufficient irradiated food into the animal diet without seriously disturbing the nutrition of the test animals giving rise to secondary toxicological findings totally unrelated to irradiation effects, and the obvious impossibility of using sufficiently large numbers of animals in each experimental group to permit ascribing with an acceptable degree of statistical confidence any observed variations to the effect of radiolytic products present in minute amounts…"
>
> "…It is more convincing to be able to state that certain likely effects have been searched for and found absent than to admit that one did not know quite what to look for – but found it absent nevertheless…"

These criticisms are equally valid for the testing of GM foods. To borrow a concept from analytical chemistry, whole-food animal studies with few experimental animals and all the confounding factors associated with interspecies variability and the lack of an identifiable test substance, have a relatively high limit of detection. Such studies require any toxic component to be either of great potency or to be present in substantial quantities in order for the study to identify their presence. Indeed, the use of animal studies with a high limit of detection (LOD) to validate or confirm compositional studies with low LODs is irrational and scientifically invalid, and would therefore appear to contravene EU animal ethics legislation on the protection of animals used for scientific purposes (EU 2010). The implausibility of gene insertion producing a *de novo* toxin, the strength of compositional and agronomic risk assessments and the inherent weaknesses of whole-food studies are such that many jurisdictions such as Australia, New Zealand, the USA and Canada have no requirement for animal studies on GM whole foods.

In classical toxicology, where pure substances or enriched preparations are tested without a specific hypothesis, dose escalation and achievement of a maximum tolerable dose (MTD) ensures that any observed effects are usually unequivocal. Where a low-toxicity substance cannot be given at sufficient dose to achieve the MTD, results at achievable doses are compared to contemporaneous historical control ranges to ensure random statistical noise is not over-interpreted. For whole-food studies, with unknown test substances, every test group is likely to be a control group and meaningful dose escalation is not possible. Therefore, classical single-substance toxicology study designs are inappropriate and such studies, if they can be ethically justified at all, must be hypothesis-based. Therefore, another key criticism of the paper is that the authors did not set out to

Table 3 Major critical errors and omissions in the Séralini et al. article (information taken in part from European Society of Toxicologic Pathology Letter to the Editor of Food and Chemical Toxicology 2012)

Category	Example	Comment
False or unsubstantiated statements	Introduction—"because of recent reviews on GMOs (Domingo and Gine Bordonaba 2011; Snell et al. 2012) we had no reason to settle at first for a carcinogenesis protocol"	This is a pre-emptive response to a justifiable critique of the study design
		Given the 2-year duration of the investigation, it is not possible that it was not already in progress (or complete) when the referenced manuscripts were published
	Table 1—Study design indicates that behavioral studies were conducted twice	No mention of behavioral studies in methods and no results presented
	Table 1—Study design indicates that ophthalmology was conducted twice	No mention of ophthalmology evaluations in the methods and no results presented
	Table 1—Study design indicates that microbiology was conducted in feces and urine	No mention of microbiology evaluations in the methods and no results presented
	Table 1—Study design indicates evaluation of Roundup^{TM} residues in tissues	No mention of tissue analysis for Roundup^{TM} in the methods and no results presented
	Table 1—Study design indicates evaluation of transgene in tissues	No mention of transgene analysis in methods or results sections, with the exception of confirmation NK603 in maize grain and formulated diets by qualitative PCR. No results presented
Incomplete or unreported test substance characterization	No reported maize grain nutrient composition and contaminant analysis results	
	No information on diet formulation and manufacturing processes	
	No information on diet nutrient composition and contaminant analysis	
	No information on drinking water contaminant analysis	
	No information on homogeneity, stability or concentration of glyphosate in drinking water formulations	
Inadequate study design to detect meaningful differences or make conclusions about tumor incidence	OECD recommends 50/sex/group, EPA recommends 50/sex/group and testing multiple mammalian species (rat and mouse) in a carcinogenicity design	
Inadequate statistical analysis of survival and tumor incidence data	Comparison of relative frequencies and total tumor burden	
	No adjustment for survival	
	No analysis of cumulative tumor risks relative to survival duration	
	No analysis of time to tumor formation	
	No discussion or presentation of test facility historical control tumor incidence data	
Control data not always included in the limited cases where data are presented to support the conclusions		

Table 3 continued

Category	Example	Comment
Summary data not presented for any response variables	Actual consumed doses of GM maize and glyphosate not reported	
	Limited data that are presented are not in original units of measurement (standardized effect scale?) and their value to the toxicologist for evaluation of potential effects, or lack thereof, is limited	
	Enzyme induction data discussed in results, but not presented for review	
Data presentation deficiencies	No standardized sampling or quantification of reported liver ultrastructural changes. Lack of bias control. Would need to consider stereologic methods for proper evaluation of ultrastructural endpoints	
	Incomplete presentation of study data (acknowledged by the authors) precludes meaningful review and evaluation of study results. Speculate that this may have been intentional?	
	Histopathology incidence/severity data not presented	
	No histopathology peer review	
	Images in Figure 3 are highly selective (tumors were observed in control rats as well, but control images were not included). Gross images of standard spontaneous tumors do not add to the overall interpretation of the study	
Low quality and erroneous histopathology analysis	Misclassification of nephroblastomas as Wilm's tumors and misinterpretation of a spontaneous early onset tumor as treatment related	These are very early onset tumors and a relationship to treatment is implausible, and not addressable from a study of this design. Attribution to treatment is either disingenuous or inept
	Failure to present tables of neoplastic incidences	This is standard practice and the statement in the paper that not all data can be shown is disingenuous. This is particularly clear when electronic supplementary material can readily be made available
	Grouping of dissimilar tumor types	Combining the incidence of mammary fibroadenomas, galactoceles and adenocarcinomas has no scientific or risk assessment basis
	Erroneous combining of degenerative findings (necrotic foci of the liver) and proliferative findings (clear cell foci, basophilic foci with atypia)	
	Misattribution of adaptive findings as adverse	Increased prevalence of endoplasmic reticulum in electron micrographs is not an adverse effect of treatment. Where a relationship to treatment is identified the finding is an adaptation to the xenobiotic load

Table 3 continued

Category	Example	Comment
Unethical treatment of animals and inhuman use of animals for propagandizing	Whole body photographs presented in the paper clearly show animals that have been allowed to suffer well beyond the point where they should have been euthanized	The tumors shown at an advanced stage are disturbing but irrelevant to the interpretation of the study as these are common spontaneous tumors in this strain of rat
	Selective presentation of photographs of treated animals but not of control animals is a clear misuse of data to present a biased interpretation	
Administered diet not characterized	Control maize line not identified	There is a greater degree of genetic variation between strains of maize than between humans and chimpanzees. Failure to clearly and comprehensively identify the strain of maize used as the control is therefore a significant deficiency

investigate a specific hypothesis, e.g. that NK603 is a mammary tumorigen. Had they done so, it would be necessary to consider the background incidence of tumors in various species/strains, to select the most relevant animal model (one with a low background incidence to minimize the signal-to-noise ratio) and to determine the group sizes necessary to provide the appropriate statistical power to identify any effects against known background variation. A scholarly consideration of the study design for such a hypothesis would not have suggested Sprague-Dawley rats and would have required much larger numbers of animals in each group. This particular rat strain exhibits a 45–80 % incidence of spontaneous tumors in the absence of any exogenous factor, depending on the diet and whether or not fed ad libitum (Prejean et al. 1973; Davis et al. 1956; Keenan et al. 1996; Suzuki et al. 1979; Thompson et al. 1961). The rats normally begin developing these spontaneous tumors after 90 days, and are used in shorter-term experiments to ascertain tumorigenicity, i.e. if tumors are formed before 90 days, then a compound is perceived to be tumorogenic. Appropriate rat strains have been used previously in long-term toxicity studies (Kano et al. 2012; Otabe et al. 2011). The Séralini article therefore suffers from all the problems of an underpowered statistical fishing trip. To an unbiased observer, the inverse dose relationship or absence of any dose relationship as seen in the tumor incidence table (reproduced here in Table 2) is almost certainly random statistical noise.

Apparent author bias

There is evidence of author bias and predetermination of outcome in the introduction of the Séralini article. For example, they suggest that 90-day toxicity studies are incomplete and inadequate, yet cite "significant disturbances induced by GMO sub-chronic toxicity studies" performed by the same authors with no acknowledgement, let alone rebuttal, of the voluminous criticisms of the self-cited papers. Nor do the authors acknowledge the large body of data, both toxicological and compositional, that has failed to reveal any toxicologically-significant differences between GM and non-GM crops (e.g. Arjó et al. 2012; Chassy 2010; He et al. 2009; Liu et al. 2012; MacKenzie et al. 2007; Tang et al. 2012; Zhu et al. 2012), including a meta-analysis also published in *Food and Chemical Toxicology*. They claim to have published the only long-term experiment, yet an uncited study using a more logical rat strain and 50 rats per treatment instead of the 10 used by Séralini and colleagues revealed no toxicity (Snell et al. 2012). An additional study not cited by Séralini and colleagues reports the results of a 104-week feeding study using transgenic soybeans in F344 rats, again with no adverse effects (Sakamoto et al. 2008).

Later in the paper, a significant number of references were cited to support the noxious effect of Roundup, but these data were obtained using isolated human hepatocytes, some originating from tumors. These models, although useful to explore mechanisms

of known effects, cannot be used to rebut the wealth of in vivo experimental data in various animal species showing that Roundup has no effect at much larger doses than supposedly administered in the Séralini article. The scientific evidence offered by these cell-based models is limited by the artificial nature of assays using single cells under non-physiological conditions. Indeed, many compounds that affect such cells have no effect on whole organisms.

Statistical issues

The experimental sample size used in the Séralini article does not follow international guidelines which recommend larger cohorts for chronic toxicity studies. The use of only ten animals in the control groups for a chronic/carcinogenicity study is inappropriate. Suitable cohort sizes for interventional studies can be calculated by taking account of the normal variability of a given end point, and the minimum desired significance of the expected changes (Lenth 2001). Indeed, those concerned with animal welfare are more averse to experimental designs that are inadequate to statistically answer the hypothesis being tested, than those using an adequate number, as the former is an unjustified waste of animals. No data or discussion is presented to justify the chosen sample size, and the inadequate design prevents meaningful interpretation of the results because random effects explain most of the observed phenomena. Critical reference data are also omitted e.g. the levels of Roundup normally found in maize (GM or non-GM), the levels of Roundup metabolites found in maize-derived material, the stability of Roundup after food processing, and the circulating or tissue levels of Roundup or any surrogate metabolite, which is critical for any study based on adsorption, distribution, metabolism and excretion (ADME). The researchers also assessed the presence and size of tumors without double blinding, which is the minimal expectation when judging the presence or absence of any given phenomenon by tactile evaluation. Other evaluation thresholds were also poorly defined, e.g. 25 % body weight loss (but no stated period), tumors over 25 % body weight (but no stated assessment method), hemorrhagic bleeding (but no stated location) and prostration (but no stated period or suspected cause). Perhaps more importantly, no reference was given for the validation of these techniques. Long-term toxicology tests usually generate a considerable volume of data including specific reports on specialized investigations such as histopathology and clinical pathology, and these could have been made available as supplementary material allowing the results to be evaluated in more detail by the scientific community. Although the multivariate statistical methods were described in detail, there was no justification to explain their suitability for data interpretation. Kaplan–Meier statistics (or similar methodologies) are absolutely required to analyze tumor prevalence and survival across time and populations. The use of mean centering and unit-variance could also artificially reduce the level of background variability therefore causing the significance of the observed variation to be exaggerated.

Even if these issues had been addressed, many of the initial results were not analyzed statistically at all, therefore no p values are cited in the first part of the results nor are any of the findings described as statistically significant. The subsequent sections suffer from inadequate pathological descriptions and again from the absence of statistical evaluation. The authors often erroneously equated "trends" with "significance" but in many cases actually acknowledged these limitations (e.g. on page 5: "They were not really different from controls"). Finally, OPLS-DA was used incorrectly. This technique helps to identify the best model and the significant variables in separating n groups of samples a posteriori, e.g. to separate the data across genders or other variables, but it cannot be applied a priori in the same way as principal component analysis. Globally, these results present an interesting example of what could or might be an effect, but they do not demonstrate an unequivocal relationship because the sample is non-representative.

These statistical issues are then compounded because the non-representative anecdotal results are used in the discussion to support spurious claims. For example, the authors attribute the potential effects of GM maize and Roundup to endocrine disruption and/or oxidative stress, without any empirical evidence. They also state that GM maize and Roundup can induce necrotic and/or apoptotic changes, but they do not show any evidence to support these statements.

Toxicity of glyphosate

Perhaps the most revealing aspect of this report is the claimed toxicity of glyphosate (Roundup) in drinking

water (0.1 ppb of Roundup or 50 ng/L of glyphosate) with the highest incidence of tumors supposedly found in the animals administered the lowest dose. These conclusions are not only implausible, but they are entirely discordant with the body of literature already available for glyphosate. Well-designed chronic toxicity studies in multiple species using doses of herbicide orders of magnitude higher than those tested by Séralini and colleagues have demonstrated no toxic effects. Indeed, a health-based value of 0.9 mg/L has been established by the World Health Organization, concluding that the presence of glyphosate in drinking-water does not represent a hazard to human health (WHO 2011). The pattern of results reported by Séralini and colleagues reflects the poor study design and the misrepresentation of random variations between groups.

Evidence for the safety of GM maize

The producers of maize-based rat feed in North America do not specifically exclude GM maize, so if these results were genuine then there would be a trend towards a greater incidence of mammary tumors across all rat species used in routine testing. Of course, this is not the case. Furthermore, GM maize is used as a staple feed for the breeding of a wide range of domestic animals including cattle, pigs, chickens and sheep, even in the EU where the cultivation of GM maize is discouraged or prohibited. Were any of the Séralini data genuine, major producers of breeding livestock could not have failed to notice and report similar phenomena.

How flawed science affects society, public opinion and policy

The continuous scientific and technological advances of the last two centuries have directly improved human health and well-being and have influenced social, economic and cultural trends. Most people consider science to be largely beneficial. These same people are aware that science can have negative effects, and that science can and does fail. The failure can be as spectacular as a nuclear meltdown, or as insidious as *trans*-fats in the diet. To distinguish between beneficial and unsafe science, the public trusts peer-reviewed data published in prestigious journals which is then interpreted by the mass media and validated by regulators. Thus any publication which fails to meet high standards is a betrayal of that trust.

New findings that affect entrenched opinions and economic interests have their detractors, particularly those with a potential global impact. One of the key ethical principles of science states that "not all that can be done must be done" (Institut Borja de Bioètica 2012). Science itself is neutral, but individual scientists and their supporters inevitably have particular interests including wealth, prestige and political influence. This is why bioethics is a critical aspect of science which exists to promote best practices in interdisciplinary research (Potter et al. 1971).

Flawed science has a deleterious impact on people and society either by delaying progress towards a better quality of life or by actively working to make life worse (Fanelli 2009). It is therefore absolutely necessary to distinguish between good and necessary research that facilitates progress and flawed science that only enriches its stakeholders while harming the majority of the population.

One of the greatest challenges in the world today is food security, and we must ensure that good science that works to reduce hunger and improve the nutritional health of the human population is encouraged, without interference from extremist agendas and political expediency (Farre et al. 2010, 2011; Twyman et al. 2009). Opinion leaders therefore have special responsibility, and scientific journals must be aware of potential wider impact of their publications. The publication of papers with poorly-designed experimental procedures and consequentially erroneous conclusions can do nothing but harm society and the reputations of dedicated scientists by providing ammunition for extremists, lobbyists and single-interest groups.

Conclusions

Politicizing science

The Séralini article taken at face value presented results that suggested the public was in grave danger. The ethically correct course of action would have been to notify the relevant authorities prior to publication, but the authors failed to do so, appearing to prefer a high-impact media campaign. Furthermore, once their manuscript was accepted, the authors took another

unprecedented step by asking the journal to delay publication while they coordinated its publication with a press conference and other dissemination activities, including a video of the experiments in progress. This is clearly not standard practice and strongly suggests that the real objective of the experiments from the very beginning was to politicize science rather than present objective data to the scientific community. Clearly, the paper should never have been published and demonstrates a catastrophic failure of the peer-review system, and it is beholden on the editor of *Food and Chemical Toxicology* to retract this article.

Even a full retraction of the Séralini article will not cleanse the Internet of the inflammatory images of tumorous rats. As well as shaking public confidence in science, the continued presence of these unreliable experiments will provide ammunition for extremists and, in a worst-case scenario, will persuade politicians and regulators to tighten restrictions on GM crops even further despite the urgent need for innovative solutions to the global food security challenge.

The role and responsibility of the media

The media also has a responsibility to present balanced and factually-correct information to the public regardless of the political leanings of individual media bodies. The Catholic Church has expressed this notion very clearly in its social policy doctrine when referring to biotechnology: "Leaders in the information sector also have an important task, which must be undertaken with prudence and objectivity. Society expects information that is complete and objective, which helps citizens to form a correct opinion concerning biotechnological products, above all because this is something that directly concerns them as possible consumers. The temptation to fall into superficial information, fuelled by overenthusiasm or unjustified alarmism, must be avoided." Unfortunately, the enticement of sensational headlines ensures the media often indulges in alarmism and thus fails its responsibility to society more often than not.

The role and responsibility of scientific journals

Scientific journals comprise a sector of the media that has long recognized the importance of providing accurate information, and a consortium of the leading publishers has established the Committee on Publication Ethics (COPE) to embrace this (http://publicationethics.org/). *Food and Chemical Toxicology*, in its "Ethical guidelines for journal publication" states: "Peer-reviewed articles support and embody the scientific method. It is therefore important to agree upon standards of expected ethical behaviour for all parties involved in the act of publishing: the author, the journal editor, the peer reviewer, and the publisher. The publisher has a supporting, investing and nurturing role in the scholarly communication process and is also ultimately responsible for ensuring that best practices are followed."

Elsevier states that it takes its duties of guardianship over the scholarly record very seriously: "Our journal programs record 'the minutes of science' and we recognize our responsibilities as the keeper of those 'minutes' in all our policies, including the guidelines we have adopted to support editors, reviewers and authors in performing their ethical duties." They go on to say "Authors of reports of original research should present an accurate account of the work performed as well as an objective discussion of its significance. Underlying data should be represented accurately in the paper. A paper should contain sufficient detail and references to permit others to replicate the work. Fraudulent or knowingly inaccurate statements constitute unethical behavior and are unacceptable." The publication of the Séralini article raises an important question as to whether the editors of *Food and Chemical Toxicology*, and by extension the publisher, have followed their own guidelines. All insist that they adhere to COPE standards, which include several that are relevant to the case in hand:

- From http://publicationethics.org/files/u2/New_Code.pdf: "Ensuring the integrity of the academic record. Whenever it is recognized that a significant inaccuracy, misleading statement or distorted report has been published, it must be corrected promptly and with due prominence. If, after an appropriate investigation, an item proves to be fraudulent, it should be retracted. The retraction should be clearly identifiable to readers and indexing systems."
- From http://publicationethics.org/files/u2/Best_Practice.pdf:
  - "(7) Editorial and peer-review processes: ensure that people involved with the editorial process (including themselves) receive adequate training and keep abreast of the latest

guidelines, recommendations and evidence about peer review and journal management keep informed about research into peer review and technological advances"

- "(10) Encouraging academic integrity. Request evidence of ethical research approval for all relevant submissions and be prepared to question authors about aspects such as how patient consent was obtained or what methods were employed to minimize animal suffering…" "…ensure that reports of experiments on, or studies of, animals cite compliance with the US Department of Health and Human Services Guide for the Care and Use of Laboratory Animals or other relevant guidelines."

Recommendations

We do not advocate retraction of scientific papers simply in response to public pressure. However, the publication of the Séralini article was a clear and egregious breach of the standards of scientific publishing and a grave insult to the integrity of thousands of dedicated scientists around the world. We therefore call upon the editor of *Food and Chemical Toxicology* to issue formal retraction of the Séralini article, at the very least in order to comply with COPE guidelines. We note that simply publishing letters to the editor pointing out the deficiencies with the paper does not relieve the editor, the journal or its publisher from the need to abide by COPE guidelines.

The publication of the Séralini article undermines the value of peer review, encouraging the plurality of opinion and democracy in science and promoting their influence on scientific policies. Therefore, we also recommend that all journal editors abide by COPE guidelines in order to protect the credibility of the peer review process and protect the integrity of the scientific process in the public view. Although COPE guidelines should be sufficient for proper editorial decisions, we also call upon all editors to recognize that their decision to publish certain papers can have serious repercussions, including the introduction of unnecessary new regulations, the escalation of expenditure in the search to ensure compliance, the unfair suppression of promising technologies and unnecessary alarmism that affects the most vulnerable members of our society.

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