Review

Characterization of scientific studies usually cited as evidence of adverse effects of GM food/feed

Miguel A. Sánchez1,* and Wayne A. Parrott2

1Asociación Gremial ChileBio CropLife, Santiago, Chile
2Department of Crop and Soil Sciences, University of Georgia, Athens, GA, USA

Received 27 April 2017; revised 30 June 2017; accepted 11 July 2017.
*Correspondence (Tel. +56-222354001; email masanchez@chilebio.cl)

Keywords: GMO, GM food/feed safety, scientific studies, evidence.

Introduction

Concerns over the lack of safety of genetically modified (GM) crops are used as arguments to ban them, or at least to regulate them heavily. Many citizens, politicians and countries generally take those arguments to reinforce misconceptions about GM crops. Anecdotal and newspaper reports also reinforce an anti-GM stance (Wunderlich and Gatto, 2015). Usually, the debate is driven by political and ideological arguments instead of science-based discussion (Trewavas and Leaver, 2001). Some aspects of agriculture in general, such as herbicides, monocultures and intellectual property, also contribute to concerns over GM crops driven by political and ideological arguments instead of science-based discussion (Trewavas and Leaver, 2001). Some aspects of agriculture in general, such as herbicides, monocultures and intellectual property, also contribute to concerns over GM crops, which are used as arguments to ban them, or at least to regulate them heavily. Many citizens, politicians and countries generally take those arguments to reinforce misconceptions about GM crops. Anecdotal and newspaper reports also reinforce an anti-GM stance (Wunderlich and Gatto, 2015).

Although referred to monolithically as GM crops in conversation, GM crops are quite distinct from each other; the only thing in common they share with each other is the process—recombinant DNA—used to produce them. Each individual use of recombinant DNA to produce a GM crop is known as an ‘event’. In the United States, the FDA has reviewed 153 events to date (http://www.accessdata.fda.gov/scripts/fdcc/?set=Biocon), many of which are on soya bean 40-3-2 and represent 60% of all studies assessed.

About the papers evaluated

The papers selected for study include those cited in four reviews of adverse effects of GM crops (Domingo and Bordonaba, 2011; Dona and Arvanitoyannis, 2009; Maña-Gómez and de la Barca, 2009; Seralini 2011). References cited in the Internet by GM Free USA, Coalition for a GM Free India and GM Watch were added.

The geographical origin of the 35 studies is striking. There are more studies published in English, 31% (11) were published in Spanish, 33% (12) in French, 14% (5) in Italian, 7% (2) in German and 5% (2) in Portuguese.

All of these papers were published in English, with the exception of two papers (14%) published in Spanish and 14% (2) in French. The geographic distribution of the studies is as follows: North America, 11% (4); Europe, 43% (15); Asia, 33% (12) and South America, 7% (3).

The most frequent author on these publications, having co-authored 11 of 35 studies (31%), is the Malatesta group at the University of Urbino and University of Verona, Italy. Nine of their articles are on soya bean 40-3-2 and represent 60% of all studies evaluated in this study.
| Main author          | Year | Journal                  | F  | Crop   | Trait | Event   | Model     | Claimed impact: health                      | Main shortcomings                                                                 |
|----------------------|------|--------------------------|----|--------|-------|---------|-----------|---------------------------------------------|-----------------------------------------------------------------------------------|
| Abdo et al.          | 2014 | Food Nutr Sci            | ni | Maize  | IR    | MON810  | Rat       | Hepatic alterations                        | No nutritional analysis of diet; no measure of mycotoxin content; no information on crop source |
| Ayyadurai & Deonikar | 2015 | Agric Sci                | ni | Soya   | HT    | nm      | In silico | Accumulation of formaldehyde; depletion of glutathione | No data supporting the study                                                                 |
| Battistelli et al.   | 2008 | Microsopie               | ni | Soya   | HT    | 40-3-2  | Mouse     | Pancreatic alterations                      | No nutritional analysis of diet; soflavone content not measured; no information about varieties used |
| Battistelli et al.   | 2010 | Eur J Histochem          | 1.809 | Soya   | HT    | 40-3-2  | Mouse     | Intestinal alterations                      | No nutritional analysis of diet; soflavone content not measured; no information about varieties used |
| Brasil et al.        | 2009 | Anat Rec (Hoboken)       | 1.490 | Soya   | nm    | nm      | Rat       | Ovary and uterus alterations                | No nutritional analysis of diet; no information on crop source                       |
| Carman et al.        | 2013 | J Org Sys (Hoboken)      | ni | Maize, Soya | HT, NK603, MON863, MON810, 40-3-2 | Pig      | Higher rate of severe stomach inflammation; thicker uterus | No nutritional analysis of diet; soflavone content not measured; no information about varieties used |
| Cisterna et al.      | 2008 | Eur J Histochem          | 1.629 | Soya   | HT    | 40-3-2  | Mouse     | Decrease of pre-mRNA transcription in 2-, 4-, 8-cell embryos | No nutritional analysis of diet; no information on crop source |
| de Vendomois et al. | 2009 | Int J Biol Sci           | 2.865 | Maize  | HT, IR NK603, MON863, MON810 | Rat       | Hepatorenal alterations                     | Flawed statistics (fishing for significance)                                                                 |
| El-Kholy et al.      | 2014 | Nutrients                | 3.270 | Soya   | nm    | nm      | Rat       | Increase in serum level of lipid peroxidation; decrease in glutathione transerase; cytogenicity | No use of non-GM soya bean as control                                                                 |
| El-Shamei et al.     | 2012 | J Am Sci (Hoboken)       | ni | Maize  | IR    | MON810  | Rat       | Histopathological changes of liver, kidney, tests, spleen and small intestine | No nutritional analysis of diet; no measure of mycotoxin content; no information on crop source |
| Ewen & Pusztai       | 1999 | Lancet                   | 10.197 | Potato | IR    | nc      | Rat       | Differences in the thickness of the gut epithelium | Inadequate sample size; protein-deficient diet; no dose-response studies; lack of proper controls |
| Fares & El-Sayed     | 1998 | Nat Toxins               | 0.691 | Potato | IR    | nc      | Mouse     | Intestinal alterations                      | Cause and effect not established                                                                 |
| Finamore et al.      | 2008 | J Agr Food Chem          | 2.562 | Maize  | IR    | MON810  | Mouse     | Immune response                            | Mycotoxins above maximum allowed (food standards)                                                                 |
| Gab-Alla et al.      | 2012 | J Am Sci (Hoboken)       | ni | Maize  | IR    | MON810  | Rat       | Differences in organ/body weight, changes in serum biochemistry | No nutritional analysis of diet; no measure of mycotoxin content; no information on crop source |
| Ibrahim & Okasha     | 2016 | Exp Toxicol Pathol       | 1.716 | Maize  | IR    | MON810  | Rat       | Histopathological changes of small intestine | No nutritional analysis of diet; no measure of mycotoxin content; no information on crop source |
| Kiliç & Akay         | 2008 | Food Chem Toxicol        | 2.321 | Maize  | IR    | nm      | Rat       | Hepatorenal alterations                     | No biological relevance (no health concerns after three generations) |
| Kiliçgün et al.      | 2013 | J Clin Anal Med          | ni | Maize  | IR    | nm      | Rat       | Alterations in length, height and weight of organs; alterations in haematology values | No nutritional analysis of diet; no measure of mycotoxin content; no information on crop source |
| Magaña-Gómez et al. | 2008 | J Appl Toxicol           | 2.127 | Soya   | HT    | 40-3-2  | Mouse     | Pancreatic alterations                      | No information on crop source and varieties used                                                                 |
| Malatesta et al.     | 2002 | Cell Struct Funct        | 0.872 | Soya   | HT    | 40-3-2  | Mouse     | Hepatic alterations                         | No nutritional analysis of diet; soflavone content not measured; no information about varieties used |
| Malatesta et al.     | 2002 | J Anat                  | 1.660 | Soya   | HT    | 40-3-2  | Mouse     | Pancreatic alterations                      | No nutritional analysis of diet; soflavone content not measured; no information about varieties used |
| Main author | Year | Journal | IF | Crop | Trait | Event | Model | Claimed impact health | Main shortcomings |
|-------------|------|---------|----|------|-------|-------|-------|-----------------------|------------------|
| Malatesta et al. | 2003 | Eur J Histochem | 1.041 | Soya | HT | 40-3-2 | Mouse | Pancreatic alterations | No nutritional analysis of diet; isoflavone content not measured; no information about varieties used |
| Malatesta et al. | 2005 | Eur J Histochem | 0.990 | Soya | HT | 40-3-2 | Mouse | Hepatic alterations | No nutritional analysis of diet; isoflavone content not measured; no information about varieties used |
| Malatesta et al. | 2008 | Histochem Cell Biol | 2.320 | Soya | HT | 40-3-2 | Mouse | Hepatic alterations | No nutritional analysis of diet; isoflavone content not measured; no information about varieties used |
| Oraby et al. | 2015 | Turk J Biol | 1.343 | Maize; Soya | nm | nm | Rat | Genotoxicity in germ and liver cells | Different control diet (wheat) |
| Prescott et al. | 2005 | J Agr Food Chem | 2.507 | Pea | IR | nc | Mouse | Immune response | Results are not specific to biotechnology |
| Sagstad et al. | 2007 | J Fish Dis | 1.712 | Maize | IR | MON810 | Salmon | Immune response | Presence of mycotoxins in the experimental diet |
| Séralini et al. | 2007 | Arch Environ Con Tox | 1.620 | Maize | IR | MON863 | Rat | Hepatorenal alterations | Flawed statistics (fishing for significance) |
| Séralini et al. | 2014 | Env Sci Eur | ni | Maize | HT | NK603 | Rat | Hepatorenal alterations; tumour rate altered | Nonappropriate animal model; flawed statistics; inadequate sample size |
| Trabalza-Marinucci et al. | 2008 | Livest Sci | 1.091 | Maize | IR | BT176 | Sheep | Hyperplasia of ruminal epithelial basal cells; higher immune response to S. abortus ovis | No measure of mycotoxin content; no information on crop source |
| Tudisco et al. | 2006 | Anim Sci | 1.021 | Soya | HT | 40-3-2 | Rabbit | Lactic dehydrogenase increased in kidney and heart | Possible plagiarism; no biological relevance |
| Tudisco et al. | 2007 | Ital J Anim Sci | 0.218 | Soya | HT | 40-3-2 | Goat | Transgene fragments detected in tissues | No biological relevance |
| Tudisco et al. | 2010 | Animal | 1.721 | Soya | HT | 40-3-2 | Goat | Transgene fragments detected in tissues; lactic dehydrogenase increased | Retracted because of plagiarism; no biological relevance; no information on crop source |
| Tudisco et al. | 2015 | Small Rum Res | 1.125 | Soya | HT | 40-3-2 | Goat | Decrease in growth performances of goats; transgene fragments detected in colostrum | No information on crop source; information about varieties used |
| Vecchio et al. | 2004 | Eur J Histochem | 0.845 | Soya | HT | 40-3-2 | Mouse | Tests alterations | Possible plagiarism; no information on crop source; no information about varieties used |
| Yum et al. | 2005 | Allergy Asthma Proc | 0.733 | Soya | nm | nm | Human | Allergy (not according to the authors) | No information on crop source; inadequate sample size |

ni, not indexed; nm, not mentioned; nc, noncommercial; IF, impact factor (year of publication).
suggesting adverse effects from this event. Their studies on maize events BT176 and NK603 were co-authored with the M. Trabalza-Marinucci (Università degli Studi di Perugia, Italy) and G-E. Séralini (University of Caen, France) teams, respectively. R. Tudisco and F. Infascelli (both from University of Naples Federico II) were part of four studies (11%), all of which assessed soya bean 40-3-2. Altogether, 87% of all studies on event 40-3-2 come from the Malatesta and Infascelli groups. G-E. Séralini was the corresponding author in three studies (9%) on different events of GM maize, corresponding to 25% of all studies assessing GM maize.

Because of the relevance of food safety, any well-conducted study under rigorous standards of scientific quality and showing adverse effects of any GM food/crop could and would be published in the most prominent journals. However, most studies often used in the public debate against GM food/crops have been published in journals with lower visibility; eight were even published in journals without a listed impact factor (Table 1).

The only study published in a high-ranking journal has been that of Ewen & Pusztai (1999) (see Table 1). However, something usually not mentioned in the public debate is that editors published an accompanying analysis highlighting the study’s flaws in many aspects of design, execution and analysis (Kuiper et al., 1999). Furthermore, the editor, Richard Horton, stated that publication of Ewen and Pusztai’s findings was not a ‘vindication’ of Pusztai’s claims. Horton argued if the study was not published, a critical evaluation of the results could not be conducted. He also cited a reviewer pointing out that he ‘would like to see the work published in the public domain so that fellow scientists can judge for themselves... if the paper is not published, it will be claimed there is a conspiracy to suppress information’ (Horton, 1999).

**Conflicts of interest**

All 35 studies declared no competing interests. Financial COIs arise when research is fully or partially funded by a party with a stake in the development of GM crops or in activities anti-GMO, whereas professional COIs arise when at least one author is affiliated with a company developing GM crops or anti-GMO institutions, even if the research is supported through public funding. Upon our examination, fewer than half—14 of 35 (40%) —show no financial or professional COIs. It is worth noting that in the most of the cases, conflicts cannot be discerned unless an author mentions if he or she is affiliated with declared anti-GMO institutions. The proportion of these 35 studies truly without a COI is somewhat lower than that for the vast majority of scientific studies supporting the safety of GM crops food/feed, where at least 406 of 698 reports (58.3%) have no financial or professional COIs (Sanchez 2015).

Overall, research for which the authors did not provide funding information represents 49% of the total reports (17 articles). Four of 35 articles (11%) had COIs either in terms of the author affiliation or funding source. The three studies from Seralini’s group were supported by the Committee of Independent Research and Information on Genetic Engineering (CRIIGEN),
which is financed by the Charles Léopold Mayer Foundation for the Progress of Humankind (FPH). This foundation has publicly supported anti-GMOS initiatives like InfOGM, Foundation Sciences Citoyennes, the European Network of Scientists for Social and Environmental Responsibility (ENSSER), Combat Monsanto and Stop OGM, among others (http://alerte-environnem.nt.fr/2012/11/12/etude-anti-ogm-de-saralini-les-petits-soldats-de-la-fondation-pour-le-progres-de-l-homme). Likewise, Greenpeace partially funded the two studies (Sérailini et al., 2007; de Vendomois et al., 2009) that found hepatorenal effects.

Although not considered in the analysis, it is worth noting that conflict of interest may have been involved in the review process of the retracted and criticized Sérailini et al. (2012) study. J.L. Domingo, author of another review here assessed (Domingo and Bordonaba, 2011), was an editor of Food and Chemical Toxicology when the Seralini study was accepted.

Carman et al. (2013) also present COIs. George Kailis, an organic food entrepreneur having a cautionary approach to GMO (http://www.farmweekly.com.au/news/agriculture/agribusiness/gene ral-news/technology-must-benefit-the-consumer-kailis/10451.aspx), partially funded the study. Furthermore, Verity Farms, another funder, has a non-GMO grain-marketing venture in the USA, and it is catalogued in the Non-GMO Sourcebook, which is a directory of non-GM food and agricultural products (http://www.nong mosourcebook.com/non-gmosourcebook/non-gmo-company.php? company=Verity+Farms). Plus, assistance is acknowledged from John Fagan, Arpad Puzstai and Jeffrey Smith, among others, three recognized opponents of GMO.

### Scientific quality of the studies

In general terms, all papers analysed here violate at least one of the basic standards for assessment of GM food/feed safety (Bartholomeaues et al., 2013; European Food Safety Authority (EFSA), 2011; ILSI 2008, 2004; Kuper et al., 2001; Codex Alimentarius Commission (www.codexalimentarius.org)):  

1. The control and experimental varieties should be isogenic and should have the same origin (i.e. grown in the same field, under similar conditions and in the same season) to diminish differences in nutritional content of control and experimental diets;

2. A proper statistical test should be selected before the study and not change it for convenience throughout the experiments. Furthermore, statistically significant differences are not necessarily biologically significant due to the normal range of physiological parameters among the organisms of the same species; and

3. If some differences or alterations are observed in a well-designed study assessing GM diets, then it is necessary to contrast it with similar previous studies—if they exist—that do not show the same effects. The discrepancy should be addressed with a plausible hypothesis explaining the causes of the nonreproducibility.

Three of 35 studies (9%) did not do any experimentation either and report results solely based on statistical re-analysis of previously published data. Sérailini et al. (2007) and de Vendomois et al. (2009) suggest hepatorenal effects on rats fed GM maize. According to the authors, the use of standard statistics does not show significant changes; rather, the parameters fell within the normal range for control animals. Therefore, the authors used a nonconventional statistical method to show significant effects at low doses but not at higher doses of exposure to GM maize. These findings do not fit the standard dose–response expected in toxicology (Wilson et al., 2001), a fact that was dismissed by the authors, who stated they ‘considered equally important effects that were neither time nor dose related’.

Likewise, Ayyadurai and Deonikar (2015) claim that algorithms developed by them predict that GM soya bean has increased formaldehyde and decreased glutathione relative to non-GM soya bean. Thus, they concluded that current safety assessment for GM food/crops is not adequate, given that formaldehyde has not been detected nor evaluated so far. The authors never validated their formulas by comparing GM and non-GM soya beans for their formaldehyde content. Instead, the authors developed their formulas by searching ‘online databases including PubMed and Google Scholar’, and data from over six thousand studies were included, but the origin of the data and their validity are unknown (European Food Safety Authority (EFSA), 2015).

The Malatesta group has been involved in nine of 35 studies (26%). This series of studies is full of methodological flaws (Table 1), but perhaps the critical point is that the level of isoflavonones in the soya bean diets was never measured. Such measurements are essential because these molecules can modulate the physiology of mammals due to the similarity they have with female sexual hormones (Brown and Setchell, 2001; Thigpen et al., 2004) and are known to be highly variable between soya bean varieties and locations (Eldridge and Kwolek, 1983).

Four studies (11%) belong to Professor Infascelli’s group. Recently, Infascelli’s group was informed that two papers from his group (Tudisco et al. 2010 and Mastellone et al., 2013, not assessed here) have been retracted. The articles intended to show that GM feed is detectable as GM DNA in goat kids and that these have abnormal gamma-glutamyl transferase activity. The University of Naples Federico II, where the studies took place, conducted its own investigation and reprimanded the authors (http://napoli.repubblica.it/cronaca/2016/02/09/news/universita...-133079638/?refresh_ce%3C/a). It concluded that multiple image heterogeneities were likely attributable to digital manipulation, raising serious doubts about the reliability of the findings. The retraction notice that was posted by the journal for Mastellone et al. (2013) specifically cites fraud. Additional details on these publications are posted on PubPeer at https://pubpeer.com/search?q=tudisco&sessionid=B66D1BF6E6DF5224 777&commit=Search+Publications (Accessed 12 March 2017).

Finamore et al. (2008) reported that ingestion of GM maize provokes an immune response in mice. Although mycotoxins can affect the immune system (Sobrova et al., 2010), the authors dismissed a mycotoxin effect arguing the levels were modest and were only slightly higher than the maximum allowable concentration. In reality, the amount was twofold (1300 vs. 750 μg/kg) higher than allowed for deoxynivalenol.

Trabalza-Marinucci et al. (2008) provide even fewer details. The authors did not mention the variety of maize used as the control, nor its origin, and mycotoxins are not addressed. In Magaña-Gómez et al. (2008), it is unclear which soya bean varieties were used and whether they were isogenic lines. The origin of the soya bean tested is not mentioned, making it impossible to evaluate inherent variability that can affect results.

Carman et al. (2013) published on pigs fed GM or non-GM diets for 22.7 weeks. There were no differences in feed intake, weight gain, mortality and routine blood biochemistry measurements. The GM diet was associated with severe stomach.
inflammation and thicker uteruses. Despite what was claimed, stomach inflammation was not tested histologically. Instead, a visual scoring of the colour of the lining of the stomach was performed, and redness was considered inflammation. It is not evident how pigs with severe stomach inflammation could have had the same weight gain as pigs with no stomach inflammation. The pattern of inflammation is likewise difficult to explain. There were more pigs with mild and moderate inflammation eating non-GM feed than GM feed. Further, there were fewer pigs with nil inflammation in non-GM feed than GM feed. In addition, although the authors classified the stomach inflammation into four visual categories, they grouped them in two for statistical analyses: severe inflammation versus nonsevere inflammation.

Uteruses of non-GM and GM-fed pigs accounted for 0.10% and 0.12% of body weight, respectively. The heaviest uterus in the GM-fed group weighed less than the heaviest uterus in the non-GM-fed group. The differences in uterus weights disappear if conventional statistical analysis is used (http://www.inexactchange.org/blog/2013/06/19/gmo-pig-study/). Finally, the authors did not provide information on the varieties of corn and soya bean used as control, and no chemical analysis of the diet was conducted (e.g. isoflavone content is unknown) to ensure the treated groups received equivalent diets.

Sérinali et al. (2012), which is a retracted and republished article (Sérinali et al., 2012), is one of the emblematic cases reporting criticized experiments. The authors claimed animals fed either GM maize or herbicide had higher tumour and mortality rates, as well as severe kidney and liver alterations. Among the most notorious flaws according to Arjó et al., 2013 are as follows: (i) the tumour rate reported is within the normal tumour rate for rats Sprague Dawley; (ii) inappropriate use of statistics: when the statistics are corrected for multiple comparisons, the negative effects disappear; (iii) inadequate sample size: that is, 10 rats per group instead of 20 rats for chemical toxicity studies, 50 rats for carcinogenicity studies and 65 rats if the survival of them is less than 50% at 104 weeks; (iv) no dose–response relationship as is expected in toxicology; (v) biased results: that is, paper contained pictures of treated rats with huge tumours, but no pictures of control group rats which had the same tumours; and (vi) the results go against an overwhelming body of evidence to the contrary.

There are several cases that do not need an extensive analysis. For instance, Orgbö et al. (2015) reported health hazards linked to the ingestion of diets containing GM maize and GM soya bean. The control animals were not treated equally and instead were fed a diet of wheat.

El-Kholy et al. (2014) investigated the effect of extra virgin olive oil and GM soya bean in rodents. However, the study aimed to compare only olive and soya bean, instead of GM and non-GM soya bean, so no conclusions are possible.

Brasil et al. (2009) designed a study to compare the effects of a prolonged use of organic and GM soya bean on the lipid profile and the ovary and uterus morphology of rats. Both diets improved the lipid profile and reduced body weight, but alterations in uterine and ovarian morphology were found in animals with prolonged exposure to these diets. Although there were no differences in isoflavone content, a chemical analysis of diets was not conducted, and no information on how the crops were grown was provided. For that reason, the authors remark that small differences in diets (fat, sugar and especially protein or amino acid content) could have led to the slight differences seen between animals.

Ibrahim and Okasha (2016) evaluated the effect of GM maize on the histological structure of jejunal mucosa of adult male albino rats using different histological, immunohistochemical and morphometrical methods. Histopathological changes were claimed in the intestine. These changes are the author’s interpretation of the photographs, not the interpretation of a panel of experts. No analysis of the diet was provided, so the differences, if they are real, may be due to variations in nutrients and protein content instead of GM maize per se. Furthermore, no mycotoxin content was conducted and nothing is mentioned about the origin of crops. The same mistake was made by Gab-Alla et al. (2012), who reported significant differences in organs/body weight and serum biochemistry between rats fed GM and non-GM maize.

While the bulk of the studies have been on commercialized crops, safety studies on events that were never commercialized have also been widely reported on. Prescott et al. (2005) and Sagstad et al. (2007) studied the immunogenicity of a GM pea and adverse effects of a GM maize in salmon, respectively. It has not been possible to replicate these studies (Lee et al., 2013; Sissener et al., 2011). It is now known that pea (both GM and non-GM) elicit an immunogenic response in mice, and the results obtained in 2005 were not specific to GM pea; for salmon, the effects observed in 2007 corresponded to the effect of confounding factors (i.e. mycotoxins) instead of the GM trait. These cases highlight the importance of repeating experiments in other laboratories to confirm results, before drawing any conclusions.

Fares and El-Sayed (1998) observed adverse effects when potatoes supplemented with Bt protein—in the form of an uncharacterized crude extract from bacteria—were provided to mice. However, GM potatoes producing Bt protein did not cause significant effects. Purity and concentration of the protein in treated potatoes were not determined, and as it was a crude extract, it has impurities and other proteins unrelated to Bt.

Finally, there are some studies in which the authors remark that their results do not show health concerns, but are nevertheless cited as an example of harm. Kišić and Akai (2008) found minor histopathological and biochemical effects in rats fed GM maize, but long-term consumption over three generations did not cause health concerns. Yum et al. (2005) recognized several flaws they committed and discussed that they could not conclude GM soya bean is allergenic. Eleven years after this publication, no other studies have reported similar results.

Even well-designed studies have been misrepresented. Selective omission of details in Dona and Arvanitoyannis (2009) gives the impression of health concerns when there were none (posted at https://pubpeer.com/publications/18989835, accessed 12 March 2017). Sérinali et al. (2011) used a filtered reference from a large list of papers addressing GM food/feed, safety assessments list in their review, and suggested health concerns from papers in which the original authors concluded no negative
effects or concerns on tested animals. For instance, Zhu et al. (2004) concluded ‘the results of this 13-week dietary feeding study demonstrated that the two types of soybean meal prepared from GM herbicide-tolerant (RR) and nearly isogenic conventional soybeans were comparable in composition and nutritional value for Sprague-Dawley rats. In addition, there was no evidence of any pathologic signs of RR soybean meal even when included at a high percentage of the diet (two or three times greater than normal)’.

However, Séralini et al. cited this study pointing out GMO affected body weight increase. Moreover, Séralini et al. cited seven of 19 studies of his list as cases where statistical differences were not biologically meaningful for the original authors; however, this can be debated according to his narrative. They did not provide new statistical analysis or details from those articles.

Finally, it is helpful to put these 35 studies in the context of the larger body of literature that has used animal studies to help evaluate food and feed safety. There are at least 204 articles assessing animal health parameters, and 111 studies assessing animal performance, 106 testing nutritional equivalence and 46 addressing allergenicity (Sánchez, 2015). A summary of published data in peer-reviewed journals comparing feeds from GM plants with their isogenic counterparts and organized by food-producing animal model can be found elsewhere (Flachowsky and Reuter, 2017).

While the 35 studies showing adverse effects only tested 11 events, the 204 other articles that assess animal health evaluate 94 different events. The soya bean event 40-3-2 has been the most analysed (28 studies; 15%), along with the maize event MON810 (25 studies; 14%). In the same subset of papers, different animal models have been used, where rat (46%), mouse (26%), fish (25 studies; 14%). In the same subset of papers, different animal models have been used, where rat (46%), mouse (26%), fish (25%), pig (6%) and cow (5%) have been the most common.

At least 44 peer-reviewed articles describing 90-day subchronic toxicity feeding studies for nine crops (Ricroch et al., 2014) have been published along with 23 long-term studies and 19 multiple-generation feeding studies (Ricroch, 2013; Snell et al., 2012). No biologically relevant effects on feed intake, digestibility, fertility, performance or animal health have been reported. Furthermore, it has been noted that over 100 billion animals have consumed GM feed with no unfavourable or perturbed trends in animal health and productivity (Van Eenennaam and Young, 2014).

It is always possible that all or some of these studies failed to detect adverse effects simply because animal studies lack enough sensitivity (Bartholomaeus et al., 2013). Nevertheless, the point remains that, in contrast to the 35 studies here assessed, when the same events tested have been conducted under a robust study design—that is proper statistical analysis, controls, etc.—no adverse effects have ever been observed.

Conflict of interest

MAS is employed by ChileBio (www.chilebio.cl), which is funded by companies that develop GM crops. WAP performed public-sector-funded research with GM crops and has performed public outreach under the auspices of the ILSI International Food Biotechnology Committee and CropLife International.

References

Arjó, G., Portero, M., Piñol, C., Viñas, J., Matías-Guiu, X., Capell, T., Bartholomaeus, A. et al. (2013) 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. Transgenic Res. 22, 255–267.

Ayadurai, V.A.S. and Deonikar, P. (2015) Do GMOs Accumulate Formaldehyde and Disrupt Molecular Systems Equilibria? Systems Biology May Provide Answers. Agricultural Sciences 6(7), 630–662.

Bartholomaeus, A., Parrott, W., Bondy, G., Walker, K. and ILSI International Food Biotechnology Committee Task Force on Use of Mammalian Toxicology Studies in Safety Assessment of GM Foods. (2013) The use of whole food animal studies in the safety assessment of genetically modified crops: limitations and recommendations. Crit. Rev. Toxicol. 43(Suppl. 2), 1–24.

Brasil, I.B., Soares, L.L., Faria, T.S., Boaventura, G.T., Sampaio, F.J. and Ramos, C.F. (2009) The impact of dietary organic and transgenic soy on the reproductive system of female adult rat. Anat. Rec. (Hoboken) 292(4), 587–594.

Brown, N.M. and Setchell, K.D.R. (2001) Animal models impacted by phytoestrogens in commercial chow: implications for pathways influenced by hormones. Lab. Invest. 81, 735–747.

Carman, J.A., Vlieger, H., Ver Steeg, L., Sneller, V., Robinson, G., Clinch-Jones, C., Haynes, J. et al. (2013) A long-term toxicology study on pigs fed a combined genetically modified (GM) soy and GM maize diet. J. Organic Systems 8(1), 1–12.

de Vendémosois, J.S., Roullier, F., Cellier, D. and Séralini, G.E. (2009) A comparison of the effects of three GM corn varieties on mammalian health. Int. J. Biol. Sci. 5(7), 706–726.

Domingo, J.L. and Bordonaba, J.G. (2011) A literature review on the safety assessment of genetically modified plants. Environ. Int. 37, 734–742.

Dona, A. and Arvanitoyannis, I.S. (2009) Health risks of genetically modified foods. Crit. Rev. Food Sci. Nutr. 49, 164–175.

Eldridge, A.C. and Kwolek, W.F. (1983) Soybean isoflavones: effect of environment and variety on composition. J. Agric. Food Chem. 31, 394–396.

El-Kholy, T.A., Abu Hilal, M., Al-Abbadi, H.A., Serafi, A.S., Al-Ghamdi, A.K., Sobhly, H.M. and Richardson, J.R. (2014) The effect of extra virgin olive oil and soybean on DNA, cytogenicity and some antioxidant enzymes in rats. Nutrients 6(6), 2376–2386.

El-Shamei, Z.S., Gab-Alia, A.A., Shatta, A.A., Moussa, E.A. and Rayan, A.M. (2012) Histopathological Changes in Some Organs of Male Rats Fed on Genetically Modified Corn (Ajeeb YG). J. Am. Sci. 8(10), 684–696.

European Food Safety Authority (EFSAs). (2011). Scientific opinion. Guidance for risk assessment of food and feed from genetically modified plants. EFSAs Panel on Genetically Modified Organisms (GMO). EFSAs J. 9, 2150.

Ewen, S.W. and Puszta, A. (1999) Effect of diets containing genetically modified potatoes expressing Galanthus nivalis lectin on rat small intestine. Lancet 354(9187), 1353–1354.

European Food Safety Authority (EFSAs). (2015) EFSAs scientific advice to EC on new scientific information in relation to the risk assessment of genetically modified organisms. EFSAs Supporting Publications 12(11)EN-885.

Fares, N.H. and El-Sayed, A.K. (1998) Fine structural changes in the ileum of mice fed on delta-endotoxin-treated potatoes and transgenic potatoes. Nat. Toxins 6(6), 219–233.

Flachowsky, G. and Reuter, T. (2017) Future challenges feeding transgenic plants. Anim. Front. 7, 15–23.

Finamore, A., Roselli, M., Britti, S., Monastra, G., Ambra, R., Turini, A. and Mengheri, E. (2008) Intestinal and peripheral immune response to MON810 maize ingestion in weaning and old mice. J. Agric. Food Chem. 56(23), 11533–11539.

Gab-Alia, A.A., El-Shamei, Z.S., Shatta, A.A., Moussa, E.A. and Rayan, A.M. (2012) Morphological and biochemical changes in male rats fed on genetically modified corn (Ajeeb YG). J. Am. Sci. 8(9), 1117–1123.

Hillebeck, A., Binimelis, R., Defarge, N., Steinbrecher, R., Székács, A., Wickson, F., Antoniou, M. et al. (2015) No scientific consensus on GMO safety. Environ. Sci. Eur. 27, 4.

Horton, R. (1999) Genetically modified foods: “absurd” concern or welcome normal?” Nat. Toxins 6(6), 219–233.

ILSI. (2004) Nutritional and safety assessments of foods and feeds nutritionally improved through biotechnology: an executive summary. J. Food Sci. 69, 62–68.
Oraby, H., Kandil, M., Shaffie, N. and Ghaly, I. (2015) Biological impact of
Mastellone, V., Tudisco, R., Monastra, G., Pero, M.E., Calabrò, A.E. (2013) Assessment of GE food safety using '-omics' techniques
Kuiper, H.A., Kleter, G.A., Noteborn, P.J.M. and Kok, E.J. (2001) Assessment of the
Kuiper, H.A., Noteborn, H.P. and Peijnenburg, A.A. (1999) Adequacy of methods
Ricroch, A.E. (2013) Assessment of GE food safety using '-omics' techniques
Prescott, V.E., Campbell, P.M., Moore, A., Mattes, J., Rothenberg, M.E., Foster, N., Nicolia, A., Manzo, A., Veronesi, F. and Rosellini, D. (2014) An overview of the
Miguel A. Sánchez and Wayne A. Parrott
ILSI. (2008) Nutritional and safety assessments of foods and feeds nutritionally
Kiliç, A. and Akay, M. (2008) A three generation study with genetically
Kiliçgündüz, H., Gürsel, C., Sunar, M. and Gökşen, G. (2013) The Comparative
Kuper, H.A., Noteborn, H.P. and Peijnenburg, A.A. (1999) Adequacy of methods
Kuper, H.A., Kletter, G.A., Noteborn, P.J.M. and Kok, E.J. (2001) Assessment of the
Lee, R.Y., Reiner, D., Dekan, G., Moore, A.E., Higgins, T.J. and Epstein, M.M. (2013) Genetically modified α-amylase inhibitor peas are not specifically allergenic in mice. PLoS ONE 8, e52972.
Magaria-Gómez, J.A., Cervantes, G.L., Yepiz-Plascencia, G. and de la Barca, A.M. (2008) Pancreatic response of rats fed genetically modified soybean. J. Appl. Toxicol. 28(2), 217–226.
Magaria-Gómez, J.A. and de la Barca, A.M. (2009) Risk assessment of genetically modified crops for nutrition and health. Nutr. Rev. 67, 1–16.
Mastellone, V., Tudisco, R., Monastra, G., Pero, M.E., Calabrò, S., Lombardi, P., Grossi, M. et al. (2013) Gamma-glutamyl transferase activity in kids born from goats fed genetically modified soybean. Food Nutr. Sci. 4, 50–54. (Retracted).
Oraby, H., Kandil, M., Shaffie, N. and Ghaly, I. (2015) Biological impact of feeding rats with a genetically modified diet. Turk. J. Biol. 39, 265–275.
Prestcott, V.E., Campbell, P.M., Moore, A., Mattes, J., Rothenberg, M.E., Foster, P.S., Higgins, T.J. and Hogan, S.P. (2005) Transgenic expression of bean alpha-amylase inhibitor peas in reals altered structure and immunogenecity. J. Agric. Food Chem. 53(23), 9023–9030.
Nicolla, A., Marzo, A., Veronese, F. and Rosellini, D. (2014) An overview of the last 10 years of genetically engineered crop safety research. Crit. Rev. Biotechnol. 34, 77–88.
Ricroch, A.E. (2013) Assessment of GE food safety using ‘-omics’ techniques and long-term animal feeding studies. New Biotechnol. 30, 349–354.
Ricroch, A.E., Bosson, A. and Kunzt, M. (2014) Looking back at safety assessment of GM food/feed: an exhaustive review of 90-day animal feeding studies. Int. J. Biotechnol. 13, 230–256.
Sagstad, A., Sanden, M., Haugland, Ø., Hansen, A.C., Olovik, P.A. and Hemre, G.I. (2007) Evaluation of stress- and immune-response biomarkers in Atlantic salmon, Salmo salar L., fed different levels of genetically modified maize (Bt maize), compared with its near-isogenic parental line and a commercial suprex maize. J. Fish Dis. 30(4), 201–212.
Sánchez, M.A. (2015) Conflict of interests and evidence base for GM crops food/feed safety research. Nat. Biotechnol. 33, 135–137.
Séralini, G.E., Mesnage, R., Clair, E., Gress, S., de Vendomois, J.S. and Celler, D. (2011) Genetically modified crops safety assessments: present limits and possible improvements. Environ. Sci. Eur. 23, 10.
Séralini, G.E., Cellier, D. and 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. 52(4), 596–602.
Séralini, G.E., Clair, E., Mesnage, R., Gress, S., Defarge, N., Malatesta, M., Hennequin, D. et al. (2012) Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Food Chem. Toxicol. 50, 4221–4231. (Retracted).
Séralini, G.-E., Clair, E., Mesnage, R., Gress, S., Defarge, N., Malatesta, M., Hennequin, D. et al. (2014) Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Environ. Sci. Eur. 26(1), 1.
Sissener, N.H., Henre, G.I., Lall, S.P., Sagstad, A., Petersen, K., Williams, J., Rohlloff, J. et al. (2011) Are apparent negative effects of feeding GM MON810 maize to Atlantic salmon, Salmo salar, caused by confounding factors? Br. J. Nutr. 106, 42–56.
Snell, C., Bernheim, A., Berge, I.B., Kuntz, M., Pascal, G., Paris, A. and Ricroch, A.E. (2012) Assessment of the health impact of GM plant diets in long-term and multigenerational animal feeding trials: a literature review. Food Chem. Toxicol. 50, 1134–1148.
Sobrova, P., Adam, V., Vasaatkoiva, A., Beklova, M., Zeman, L. and Kizek, R. (2010) Deoxynivalenol and its toxicity. Interdiscip. Toxicol. 3, 94–99.
Thijssen, I.E., Setchell, K.D.R., Saunders, H.E. and Haseman, J.K. (2004) Selecting the appropriate rodent diet for endocrine disruptor research and testing studies. J. Anim. Sci. 82, 401–416.
Trabalza-Marinucci, M., Brandi, G., Rondini, C., Avelini, L., Giammarni, C., Costarelli, S., Acuti, G. et al. (2008) A three-year longitudinal study on the effects of a diet containing genetically modified Bt176 maize on the health status and performance of sheep. Livest. Sci. 113, 178–190.
Trewavas, A. and Leaver, C. (2001) Is opposition to GM crops science or politics? An investigation into the arguments that GM crops pose a particular threat to the environment. EMBO Rep. 2, 455–459.
Tudisco, R., Mastellone, V., Cutrignelli, M.I., Lombardi, P., Bovera, F., Mirabella, N., Piccolo, G. et al. (2010) Fate of transgenic DNA and evaluation of metabolic effects in goats fed genetically modified soybean and in their offspring. Anim. 4(10), 1662–1671.
Van Eenennaam, A.L. and Young, A.E. (2014) Prevalence and impacts of genetically engineered feedstuffs on livestock populations. J. Anim. Sci. 92, 4255–4278.
Wilson, N.H., Hardisty, J.F. and Hayes, J.R. (2001) Short-term, subchronic and chronic toxicology studies. In Principles and Methods of Toxicology, 4th ed. (Hayes, A.W., ed.), pp. 917–957. Philadelphia: Taylor and Francis.
Wunderlich, S. and Gatto, K.A. (2015) Consumer perception of genetically modified organisms and sources of information. Adv. Nutr. 6, 842–851.
Yum, H.Y., Lee, S.Y., Lee, K.E., Sohn, M.H. and Kim, K.E. (2005) Genetically modified and wild soybeans: an immunologic comparison. Allergy Asthma Proc. 26(3), 210–216.
Zhu, Y., Li, D., Wang, F., Yin, J. and Jin, H. (2004) Nutritional assessment and fate of DNA of soybean meal from roundup ready or conventional soybeans using rats. Arch. Anim. Nutr. 58, 295–310.