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Review

Safety assessment of GM plants: An updated review of the scientific literature

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ABSTRACT

In a wide revision of the literature conducted in 2000, I noted that the information in scientific journals on the safety of genetically modified (GM) foods in general, and GM plants in particular, was scarce. Of course, it was not sufficient to guarantee that the consumption of these products should not mean risks for the health of the consumers. Because of the scientific interest in GM organisms (GMOs), as well as the great concern that the consumption of GM foods/plants has raised in a number of countries, I conducted two subsequent revisions (2007 and 2011) on the adverse/toxic effects of GM plants. In the present review, I have updated the information on the potential adverse health effects of GM plants consumed as food and/or feed. With only a few exceptions, the reported studies in the last six years show rather similar conclusions; that is to say, the assessed GM soybeans, rice, corn/maize and wheat would be as safe as the parental species of these plants. However, in spite of the notable increase in the available information, studies on the long-term health effects of GM plants, including tests of mutagenicity, teratogenicity and carcinogenicity seem to be still clearly necessary.

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1. Introduction

Genetically modified (GM) foods, a kind of genetically modified organisms (GMOs), are foods derived from organisms whose genetic material (DNA) has been modified in an unnatural way (e.g. through the introduction of a gene from a different organism). Nowadays, available GM foods stem mostly from plants, which have been genetically modified to improve yield, through the introduction of resistance to plant diseases, or of increased tolerance of herbicides. In recent years, important social and political debates on the potential negative environmental impact of transgenic plants, as well as their health risks for the consumers have been generated, debates in which the scientific community has been also involved. During the last two decades, at least two important controversies on GM plants, popularly known as the

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affair Pusztai and the affair Séralini, have occupied an important place in the pages of scientific journals. The first one began in 1998, reaching the zenith in 1999. In brief, that "affair" was the result of the stir caused by the Árpád Pusztai's premature release of information to the mass media —previously being published in scientific journals- on the adverse effects in rats feeded with GM potatoes (Ewen and Pusztai, 1999). As result of that intense debate generated by that study and the doubts generated by some "scientific" responses that even were not supported by any experimental evidence, in 2000, I decided to review the available information on the health risks of GM foods published in scientific journals between January 1980 and May 2000 (Domingo, 2000; Domingo and Gómez, 2000). One of the most relevant -also surprising- results of the review was the absence in the databases of articles reporting studies carried out by technology companies, or studies on risk assessment conducted under the auspicious of national authorities. The lack of toxicological studies on GM plants was certainly evident. It was concluded that if data on toxicological assessment of GM foods in general, and GM plants in particular were obtained, the results had not been published in scientific journals, avoiding consequently the possibility of being subjected to the judgement of the international scientific community (Domingo, 2000; Domingo and Gómez, 2000). PubMed was the database used for that review, being genetically modified foods, toxicity of transgenic foods, adverse effects of transgenic foods, and health risks of transgenic foods the "key terms" of the search. The number of citations corresponding to each of these 4 terms was 101, 44, 67 and 3 respectively, figures clearly low.

Six years after the above indicated revision, I prepared a new review-article on the health risks of GM plants (Domingo, 2007). That new revision covered the period between January 1980 and October 2006. The "key terms" were extended to the following 12 (in parenthesis, number of citations found): genetically modified foods (686), GM foods (3498), transgenic foods (4127), toxicity of transgenic foods (136), health risks of transgenic foods (23), adverse effects of genetically modified foods (170), toxicity of genetically modified foods (38), health risks of GM foods (38), health risks of genetically modified foods (72), toxicity of GM foods (120), adverse effects of GM foods (276), and adverse effects of transgenic foods (199). It was noted that the number of references corresponding to the "key terms" used in the previous revision (Domingo and Gómez, 2000) increased very considerably. Thus, genetically modified foods passed of 101–686 citations, toxicity of transgenic foods increased from 44 to 136, adverse effects of transgenic foods went from 67 to 199, while health risks of transgenic foods increased from 3 to 23, being the citations related with general terms (e.g., genetically modified foods), quantitatively important. In contrast, references concerning specific risk assessment were much more limited (Domingo, 2007). In summary, that review on the potential toxic effects/health risks of GM plants showed that experimental data were still very scarce. Most investigations corresponded to short-term studies, mainly nutritional studies, with very limited toxicological information, while long-term toxicological studies that should guarantee the safety of the transgenic plants for animal and human consumption, were certainly very scant.

In 2010, I again assessed the state-of-the-art regarding the potential adverse effects/safety assessment of GM plants for human consumption (Domingo and Giné Bordonaba, 2011). The number of references in the used databases (PubMed and Scopus) dramatically increased since my previous revision (Domingo, 2007). The new revision covered the period between January 1980 and August 2010. For the first time, a certain equilibrium between the number of research groups suggesting that a number of varieties of GM products (mainly maize and soybeans) were as safe and nutritious as the respective conventional non-GM plants, and the researchers raising still serious concerns on the consumption of GM plants was detected (Domingo and Giné-Bordonaba, 2011). Interestingly, among the citations found, it was noted that the biotechnology companies that are responsible of commercializing these GM plants were already conducting most of these studies. Thus, that revision showed a notable advance in comparison with the lack of studies published in scientific journals by those companies in previous years.

Because of the great interest and controversy that the topic still generates in both the public opinion and the scientific community, I have updated the existing information directly related with adverse health effects of GM plants consumed as food and/or feed. As in my previous revisions, I have not here included the studies regarding allergenicity of GM plants. However, it is evident that a system of food allergy vigilance is basic, as there are GM crops that are specifically related to food sensitivity (wheat or peanuts, for example), which are of special concern in terms of public health. PubMed and Scopus have been used as databases and the period of review covered between January 2011 and May 2016. Next, the available information on rice, soybeans, corn/maize and wheat is presented.

2. GM plants

2.1. Rice

Zhou and co-workers (2011, 2014) have investigated in Sprague-Dawley (SD) rats the adverse effects of the transgenic rice line (TRS) with high amylose and resistant starch (RS) contents. In a first study (Zhou et al., 2011), a 90-day toxicology feeding experiment was conducted in animals fed with diets containing 70% of either TRS rice flour, its near-isogenic rice flour, or a control diet. Body weight, body weight gain and food consumption were measured. In addition, various pathological responses such as hematological parameters and serum chemistry, at the midterm and the end of the study, as well as urinalysis profile and serum sex hormone response at the end of the study were determined. Moreover, clinical signs, relative organ weights and microscopic observations were compared between the group given transgenic rice and its near-isogenic rice group. The combined data indicated that high-amylose TRS grain was as safe as the conventional non-transgenic rice in rats. The results also showed that the consumption of diets from transgenic TRS rice did not cause adverse effects in rats, suggesting that high-amylose TRS grain was as safe as the conventional non-transgenic rice in rats. In a subsequent investigation (Zhou et al., 2014), clinical performance, reproductive capacity and pathological responses including body weight, food consumption, reproductive data, hematological parameters, serum chemistry, organ relative weights, and histopathology were examined in a three generation reproduction study in rats consuming high-amylose transgenic rice (diet containing 70% transgenic TRS rice). It was concluded that consuming a transgenic rice diet had no adverse health effects in rats. Although some significant differences were found in the results between the rice based diet vs the standard diet group, according to the authors, these differences could be due to the differences in composition and nutrition source of the feed. The same research group also performed a three-generation study in SD rats fed high-lysine transgenic rice (LR) (diet containing 70% of this transgenic rice). Clinical performance variables and pathological responses were investigated. The results indicated that there were significant differences in some hematological and serum chemistry parameters, as well as in relative organ weights in rats consuming the transgenic rice diet -or non-transgenic rice diet- compared with the control diet. However, no macroscopic or histological adverse effects were observed. As for the TRS rice, the

authors also concluded that LR rice was as safe as near-isogenic non-transgenic rice (Zhou et al., 2012).

The effects of consuming transgenic *Bacillis thuringiensis* (*Bt*) rice were also investigated in Wistar rats by another Chinese research group. In a first investigation, Wang et al. (2013a) examined the effects of 90-day feeding of transgenic *Bt* rice TT51 on the reproductive system of male rats. Experimental groups were treated with diets formulated with either 60% TT51 (transgenic *Bt* rice) or MingHui63 (none-transgenic counterpart). Another group of rats were fed with rice-based AIN93G diet as negative control. Body weights, food intake, hematology, serum chemistry, serum hormone levels, sperm parameters and relative organ/body weights were measured, while gross as well as microscopic pathology were also examined. The results showed that TT51 did not cause adverse effects on the reproductive system of male rats when compared with animals given MingHui63 or the control rats. In a subsequent study, these authors (Wang et al., 2014a) assessed the potential reproductive effects of TT51 in two generations of male and female Wistar rats. Rice-based diets containing 60% ordinary grocery rice, MingHui63 rice, or TT51 rice by weight, were fed to two generations of male and female rats in order to determine the potential reproductive effects of TT51. Clinical performance variables and potential histopathological abnormalities in a number of tissues, including ovaries, uterus, testes and epididymis were examined. No histological changes were observed in any of the examined tissues. The results showed that TT51 did not cause significant alterations on reproduction of rats.

The results of other recent subchronic/long-term studies on the adverse/toxic effects of rice in rats have shown a similar conclusion; that is to say, based on the parameters examined, the kinds of transgenic rice assessed would be as safe as the non-transgenic rice. This statement was supported by the results of Tang et al. (2012), who conducted a 90-day dietary toxicity study of genetically modified rice T1C-1, expressing Cry1C protein, in SD rats. Also, by those of Wang et al. (2013a,b), In turn, Zhang et al. (2014) and Song et al. (2015), obtained also similar conclusions in a long-term toxicity study on transgenic rice, with Cry1Ac and sck genes, and in a 90-day subchronic feeding study of GM rice expressing Cry1Ab protein, respectively, both conducted in SD rats. Yuan et al. (2013) determined in SD rats feed with GM T2A1 rice, parameters such as microflora composition, intestinal permeability, epithelial structure, fecal enzymes, bacterial activity, and intestinal immunity. Although significant differences were noted between rice-fed groups and control groups in some parameters, no differences were detected between GM and non-GM groups. No adverse effects were found on the gastrointestinal health of rats following intake of GM T2A-1 rice. Recently, Zou et al. (2016) assessed in SD rats the safety of a newly developed insect-resistant GM rice expressing the *cry2A** gene. For it, a subchronic oral toxicity study was carried out. Animals received GM rice and non-GM into the diet at levels of 30, 50 and 70% (w/w), No treatment-related adverse or toxic effects were noted on daily clinical signs, body weight, food consumption, hematology, serum biochemistry, and organ weight, as well as on gross and histopathological examination. These results also indicated that GM rice with *cry2A** gene would be as safe for food as conventional non-GM rice.

On the other hand, the GM rice expressing human serum albumin (HSA) is used for non-food purposes. Recent studies have been conducted to assess its safety. Sheng et al. (2014) performed a subchronic toxicity study in SD rats (including also an allergenicity study in vitro) for GM rice 4-114-7 expressing pharmaceutical protein (human serum albumin). Rats received for 90 days diets containing 12.5%, 25.0% and 50.0% GM or non-GM rice (non-transgenic isogenic control "Taipei 309"). The observed changes were considered incidental biological variations, not being treatment related. In another study, SD rats were fed diets containing 50% (w/w) GM rice expressing HSA or non-GM rice for 90 days. Urine metabolites were analyzed to examine potential changes occurred in the dynamic process of metabolism, while fecal bacterial profiles were analyzed to reflect intestinal health. Short chain fatty acids and fecal enzymes were also investigated. Although some significant differences were observed in rats receiving GM rice, the changes were not significantly different from the control diet group (Qi et al., 2015).

In recent years, most studies on the effects of the diets containing GM rice have been conducted in rats. However, investigations using other species have been also performed. Li et al. (2015) evaluated in Arbor Acres female broiler chicken the effects of feeding *Bt* rice expressing the *Cry1Ab/1Ac* protein. In these animals, health status, relative organ weights, biochemical serum parameters and occurrence of *Cry1Ab/1Ac* gene fragments were determined. No adverse effects of the GM rice were observed on chicken growth, biochemical serum parameters and necropsy during the 42-day feeding period, while no transgenic gene fragments were detected in the samples of the analyzed tissues. On the other hand, some investigations have been conducted in aquatic ecosystems. Recently, Li et al. (2014) assessed the environmental effects of two Bt rice lines expressing either the *cry1Ab/1Ac* or *cry2A* genes, respectively, by using zooplanktons as indicator species under normal field management practices. Pesticides were used when required. The results showed that rice type (*Bt* and non-*Bt*) significantly influenced zooplankton abundance and diversity, being 95% and 80% lower in non-*Bt* rice fields than *Bt* rice fields. Moreover, water from non-*Bt* rice fields was significantly less suitable for the survival and reproduction of *Daphnia magna* and *Paramecium caudatum* in comparison with water from *Bt* rice fields. It was concluded that *Bt* rice is even safer to aquatic ecosystems than non-Bt rice. The microalga *Chlorella pyrenoidosa* was also used to assess the effects of leachates extracted from Cry1Ca-expressing transgenic rice (T1C-19) straw (Wang et al., 2014b). No adverse effects on the growth of *C. Pyrenoidosa* were observed.

Moreover, Wang et al. (2014c) assessed the effects of transgenic *cry1Ab/1Ac* rice (Huahui 1, HH1) on paddy frogs by comparing HH1 and MH63 (rice line Minghui 63) rice paddies, with and without pesticide treatment. Cry1Ab/1Ac protein levels were determined in tissues of tadpoles and froglets collected from the paddy fields. In turn, *rana nigromaculata* froglets were raised in purse nets placed within these experimental plots. The results showed that cultivation of transgenic cry1Ab/1Ac rice did not adversely affect paddy frogs. In a subsequent study, Chen et al. (2015) examined the potential risk posed by transgenic *cry1Ca* rice (T1C-19) on the development of a frog species by adding purified Cry1Ca protein or T1C-19, rice straw into the rearing water of *Xenopus laevis* tadpoles, and by feeding *X. laevis* froglets diets containing rice grains of T1C-19 or its non-transformed counterpart MH63. No significant differences among groups were found in terms of time to complete metamorphosis, survival rate, body weight, body length, organ weight and liver enzyme activity, after being exposed to the Cry1Ca. No significant differences were also detected in the mortality rate, body weight, daily weight gain, and liver and fat body weight of the froglets between the T1C-19 and MH63 dietary groups after 90 days, while no pathological changes were observed in the analyzed tissues. These results showed that planting transgenic *cry1Ca* rice should not adversely affect frog development. Zhu et al. (2015), who assessed in *Xenopus laevis* the safety for 90 days of GM rice expressing Cry1Ab/Ac protein, also concluding that frog development was not adversely affected by the intake of GM rice, a similar conclusion than that reported by Chen et al. (2015).

2.2. Soybeans

Qi et al. (2012) conducted a subchronic feeding study in SD rats, in which 7 groups of animals were fed with balanced diets containing 7.5%, 15% and 30% (w/w) GM soybean 3Ø5423 × 40-3-2 (T1, T2, T3), or traditional soybean (N1, N2, N3) and a control diet, respectively. During the exposure period (90 days), body weight and food consumption were weekly determined. In addition to nutritional and growth performance variables, analysis of standard clinical chemistry, hematology and organ variables was also carried out. Some significant differences were observed in rats fed the 3Ø5423 × 40-3-2 diet in comparison with animals fed the non-GM control diet. Notwithstanding, the authors did not consider these differences to be treatment-related, being within the normal ranges of the control group. It was concluded that the GM soybean 3Ø5423 × 40-3-2 was as safe as non-GM soybeans. Chukwudebe et al. (2012) performed in Wistar rats a subchronic study (91 days) aimed at comparing the health and nutritional profile of the CV127 soybeans (at levels of 11% and 33%), as well as the safety of these soybeans in comparison to that of its near isogenic conventional variety, and also with two other conventional soybean varieties. No treatment related adverse effects were observed on growth, food consumption, morbidity, hematology and clinical chemistry, compared to rats fed conventional soybean varieties. Only a few minor and/or significant differences were found in hematologic and organ weight parameters, between the test and control groups. Similar results were also reported by He et al. (2016), who in recent studies conducted in rats and poultry fed CV127, did not found significant differences in growth and performance response variables. Recently, Wang et al. (2016) reported the results of a 90-day subchronic toxicological study of the dicamba-tolerant soybean, MON87708, conducted for safety assessment. The potential toxicity of MON87708 was compared to that of the near isogenic non-GM soybean line A3525. Diets were prepared at levels of 7.5%, 15% and 30% (w/w) with the main nutrients of the various diets balanced and then fed to 6 groups of SD rats. There were some isolated parameters indicating significant differences in body weight, feed consumption, hematology and serum biochemistry, and relative organ weights. However, the differences were not related with test-diet dose, being attributed to incidental and biological variability. It was concluded that the transgenic soybean MON87708 was as safe as the non-transgenic isogenic counterpart (Wang et al., 2016). Taking into account that GM soybeans (GMSB) can adversely affect sperm quality and quantity, El-Kholy et al. (2015) evaluated the potential protective effect of extra virgin olive oil (EVOO) against GMSB-induced disruption in the reproductive system of male SD rats. Four groups of animals fed combined diets with GMSB (15%) and/or EVOO (30%) for 65 days. Serum zinc, vitamin E, and testosterone levels were analyzed in blood, while histopathological and weight changes in sex organs were evaluated. The results showed that EVOO ameliorated the adverse effects of GMSB on reproductive organs in adult male rats.

While most studies to test the effects of GM soybeans have been conducted in rats, other animal species have been also used. Thus, Venancio et al. (2012) assessed the antimutagenic and mutagenic properties of commercial soybeans in ale Swiss mice, which were fed diets containing 1%, 10% and 20% (w/w) transgenic soybeans (BRS Valiosa RR), or parental isogenic conventional soybeans. It was found that transgenic soybeans were non-mutagenic, having also protective effects against DNA damage similar to those of conventional soybeans (64%–101% for conventional and 23%–33% for transgenic diets). On the other hand, Herman et al. (2011) performed a 6-week broiler study with diets containing toasted DAS-68416-4 soybean meal in order to evaluate the equivalence with conventional comparators, as well as to seek for potential adverse effects. No significant differences between the groups fed diets containing conventional or transgenic soybeans were observed.

Recent studies have examined other issues, such as the ecological interactions of Roundup Ready 2 YieldR- soybean (MON 89788), without founding effects of the genetic modification that could result in increased pest potential or adverse environmental impact of that transgenic soybean (Horak et al., 2015). In turn, Fast et al. (2015) determined the nutrient and antinutrient composition of event DA-81419-2 soybean, which was equivalent to non-transgenic soybean.

2.3. Corn/maize

To assess the safety of maize BT-38, a GM maize expressing *Cry1Ac-M*, Liu et al. (2012) conducted a 90-day subchronic feeding study in SD rats, which received BT-38 in the diet, at concentrations of 12.5%, 25% and 50%. Body weight, feed consumption and toxicological response variables were measured, while gross and microscopic pathology were carried out. Neither deaths, nor adverse differences in the response variables of rats consuming diets containing GM maize BT-38 and non-GM maize were observed, concluding that BT-38 maize was as safe as conventional non-GM maize. The safety of another GM hybrid corn, DP-ØØ4114-3, was evaluated in SD rats by Delaney et al. (2013), in accordance with OECD guidelines. A 13-week feeding study was performed in 12 groups of rats. Maize grain was incorporated in all diets at 32% (w/w). No significant treatment-related differences in body weight, food consumption, clinical pathology parameters (hematology, blood chemistry, urinalysis, or organ weight) were observed between rats consuming the diets containing 4114 maize grain and animals fed conventional maize diets. However, renal tubule neoplasms were detected in two male rats consuming diets containing the 4114 maize grain (Delaney et al., 2013). Based on this result, an additional pathology study was conducted to characterize the proliferative renal tubule changes and to determine if they should be regarded spontaneous, or test diet related. An expert panel of pathologists was convened as Pathology Working Group (PWG). By unanimous opinion, the PWG concluded that the proliferative renal tubule cell lesions were spontaneous and not related to consumption of diets containing 4114 maize grain (Hardisty et al., 2013). Zhu et al. (2013), assessed in SD rats the food safety of GM maize with the G2-aroA gene (a gene that confers glyphosate herbicide tolerance to crops) in a 90-day feeding study. The safety was compared with the non-GM isogenic line. Maize grain from GM and non-GM isogenic control lines was administered into the diets at 12.5%, 25% and 50%. The parameters evaluated were body weights, food consumption, serum biochemistry, hematology, as well as absolute and relative organ weights. Gross and microscopic pathology were also carried out. None of the differences found were considered as adverse, being not related to the presence of G2-aroA maize grain. Therefore, it was concluded that the GM glyphosate-tolerant maize was as safe as conventional maize. Other 90-day oral toxicity studies on the adverse effects of two different varieties of GM maize MON810 have been conducted in Wistar Han RCC rats. It was demonstrated that the MON810 maize, at a level of up to 33% in the diet, did not induce adverse effects in rats, after subchronic exposure, independently of the two different genetic backgrounds of the event (Zeljenková et al., 2014). However, the presentation and interpretation of these last results were subjected to various serious criticisms (Bauer-Panskus and Then, 2014), requesting retraction because of a possible “manipulation” of the results. The criticisms were responded by the senior author of the group (Steinberg, 2015). After an invitation to an open scientific discussion made by the Editor-in-Chief (Hengstler, 2015) of the journal where Zeljenková et al. (2014) published their results, the

article was not finally retracted. Independently on that controversy, recently, 90-day feeding studies of transgenic BT799 and GH5112E-11C maize were conducted in Wistar and SD rats, respectively (Guo et al., 2015; Han et al., 2016). No significant differences between the GM and non-GM maize in the reproductive system of male rats were found between BT799 and Zhen58 maize, or control (Guo et al., 2015). In turn, there was also a lack of differences in the clinical signs, body weights, food consumption, hematology, clinical chemistry, organ weights and histopathology between rats consuming the GM maize and those given non-GM maize (Han et al., 2016).

The scientific controversy —as well as that in the mass media- on the safety of GM maize has been and is still important. For example, Abdo et al. (2014) reported various alterations in organ weights, hematology and serum biochemical analyses in rats fed Bt corn (MON810; Ajeeb YG) after 1.5 months, but with changes increasing after 3 months. Severe changes in the liver of Bt group after 3 months were found to be particularly relevant. In relation to these results, I would like to highlight the very low number of animals used in that study, only 6 males and females per group. However, the study on GM maize -and also on all GM plants- which has generated more controversy in the current decade was, by far, that published by Séralini et al. (2012). During 2 years, these authors investigated in SD rats, the effects of a Roundup-tolerant GM maize. The authors reported that female rats developed large mammary tumors almost always more often than -and before- controls, being the pituitary the second most altered organ. In turn, the sex hormonal balance was also modified. In males, liver congestions and necrosis were 2.5–5.5 times higher, being severe kidney nephropathies also generally 1.3–2.3 greater than those found in control animals. Males presented up to four times more large palpable tumors starting 600 days earlier than in the control group, in which only one tumor was noted. It was concluded that the results could be due to the non linear endocrine-disrupting effects of Roundup, but also by the overexpression of the transgene in the GM maize and its metabolic consequences. These results were originally published in Food and Chemical Toxicology (FCT) (Séralini et al., 2012), but the paper was retracted in November 2013 by the Editor-in-Chief of the journal, who based his decision on inconclusive data and unreliable conclusions (Hayes, 2014a,b). During the elapsed time between the publication and the retraction of that article, even sometime after the retraction, the scientific controversy was notable. A considerable number of Letters to the Editor of FCT, mainly against the results of the study, was published. Séralini et al. (2013) also published a reply to the Letters to the Editor that questioned the validity of the results and significance of their conclusions. The controversy ended with a final response of Séralini et al. (2014a) and with the paper being republished in the journal Environmental Science Europe (Séralini et al., 2014b).

In addition to the above studies in rats, throughout the period here reviewed, investigations on the safety of GM maize have been also conducted in other animal species. Thus, Stagg et al. (2012) performed acute and 28-day repeated dose toxicology studies in mice with aryloxyalkanoate dioxygenase (AAD-1) protein expressed in 2,4-D tolerant DAS-40278-9 maize. Neither acute lethality, nor adverse effects were observed in the 28-day repeated-dose dietary toxicity study, incorporating the AAD-1 protein into diets at concentrations up to 1000-fold greater than the highest estimate of human exposure to maize. Also in mice, Song et al. (2014) investigated the immunotoxicological potential of GM corn with Bt Cry1Ah gene. Mice in the GM corn group and the parental corn group were fed with diets containing 70% corresponding corn for 30 days. Immunotoxicological effects of the GM corn were assessed through a long series of immunopathology parameters According to the authors, the results did not show adverse immunotoxicological effects of the GM corn when feeding mice for 30 days. Recently, Chen et al. (2016) reported the results of a long-term toxicity study in a miniature pig model on the potential adverse effects of corn genetically modified with the *cry1Ac* gene. Animals were assigned one of the diets containing 65% non-transgenic isogenic corn, or *Bt* corn, at three stages of growth and the potential toxicological effects of transgenic corn on pigs were assessed. The results did not indicate adverse effects on the growth, immune response and health indicators at any stages of growth of the miniature pigs. On the other hand, Holderbaum et al. (2015) examined the chronic responses of *Daphnia magna* under dietary exposure to leaves of a transgenic (event MON810) *Bt*-maize hybrid and its conventional near-isoline. The *Daphnia magna* bioassay showed a resource allocation to production of resting eggs and early fecundity in *Daphnia magna* fed GM maize, with adverse effects for body size and fecundity later in life.

2.4. Wheat

In contrast to GM rice and GM maize, during the period reviewed, the published information on the safety of GM wheat has been certainly very scarce. In fact, only two papers (Liang et al., 2012, 2013) are available in the scientific literature. These studies assessed in BALB/c mice the immunotoxicological effects of GM drought-resistant wheat (Liang et al., 2012) T349 with *GmDREB1* gene and the wheat genetically modified with *TaDREB4* (Liang et al., 2013). Both studies reached the same conclusions: the GM drought-resistant wheat T349 and the GM wheat with *TaDREB4* gene were equivalent to the parental wheat in the effects on immune organs and immunologic functions of mice, not showing immunotoxicity.

3. Recent reviews in the scientific literature on GM plants

Since the publication of our previous review (Domingo and Giné Bordonaba, 2011) and until now, a number of authors have published reviews on the safety assessment of GM plants. The most relevant conclusions of these reviews are next summarized. Snell et al. (2012) revised data on the effects of diets containing GM maize, potato, soybean, rice, and triticale on animal health. The authors examined 12 long-term studies (of more than 90 days, up to 2 years in duration) and 12 multigenerational studies (from 2 to 5 generations). In general terms, no significant differences -in the parameters observed- were found in the 24 studies examined. According to this, it was concluded that he studies reviewed showed that GM plants were nutritionally equivalent to their non-GM counterparts, and therefore, they could be safely used in food and feed. Based on the results of a review on the use of whole food animal studies in the safety assessment of GM crops, Bartholomaeus et al. (2013) concluded that whole food animal toxicity studies were unnecessary and scientifically unjustifiable. According to the authors, this strong, and rather unexpected conclusion, was based on the comparative robustness and reliability of compositional and agronomic considerations, as well as on the absence of any scientific basis for a significant potential for de novo generation of toxicologically significant compositional alterations, as a sole result of transgene insertion. In contrast to this, as conclusions of their review on the safety, risks and public concerns of GM foods, Bawa and Anilakumar (2013) remarked the need of introducing novel methods and concepts to probe into the compositional, nutritional, toxicological and metabolic differences between GM and conventional crops. They also remarked the lack of trust in institutions and institutional activities regarding GMOs, as well as the public perception that institutions have failed to consider the current concerns of the public as part of their risk management activities. In the same line that Bawa and Anilakumar

(2013), in another review on the benefits and risks associated with GM food products, Kramkowska et al. (2013) indicated that examples arguing for the justified character of genetic modifications, and cases proving that their use can be dangerous, were innumerable. Consequently, these authors concluded that complex studies were indispensable which, in a reliable way, evaluated effects linked to the consumption of food produced with the application of genetic engineering techniques. Zdziarski et al. (2014) conducted a critical review on GM crops and the rat digestive tract. Interestingly, among the 21 studies detected in their search, 14 were general health assessments of the GM crop on rat health, with most of these studies having been performed after the crop had been approved for human and/or animal consumption. Half of these were published at least nine years after approval. Most studies reviewed by Zdziarski et al. (2014) detected a lack of a unified approach and transparency in their methodology and results, making impossible to properly review or repeat these studies. It was concluded, and I quite agree, that each GM product should be assessed with appropriate studies that indicate the level of safety associated with them. The necessity of establish detailed guidelines that allow the generation of comparable and reproducible studies was another interesting conclusion. Finally, Tufarelli et al. (2015) reviewed recently the safety, performance and product quality of GM feeds in poultry diet, concluding that GM feeds were substantially equivalent, resulting as safe as existing conventional feeds.

4. Conclusions

Firstly, I would highlight the considerable increase in the available information on the potential adverse/toxic effects of GM foods in general, and GM plants in particular, between our first search (Domingo, 2000; Domingo and Gómez, 2000) and the current one. In my third revision on this topic (Domingo and Giné Bordonaba, 2011), we commented that a certain equilibrium had been reached in the number of published studies that were conducted by biotechnology companies and those performed by independent research groups, without –in principle- any relationship with the companies responsible of commercializing the GM crops. According to the results of the current search, the edible plants whose safety has been assessed/reported during the last 5–6 years, have been basically soybeans, corn/maize, rice and wheat, being the information about wheat limited only to a couple of immunotoxicological studies. As it already happened in our previous review (Domingo and Giné Bordonaba, 2011), since 2006 (Domingo, 2007), there are not new reports in the scientific literature about GM potatoes, tomatoes, cucumber, peas, etc. In this sense, it is interesting to note that the first great controversy on GM plants was due to the publication of the results of Ewen and Pusztai (1999), who examined in rats the effects of diets containing GM potatoes. These authors found variable effects on different parts of the gastrointestinal tract of the animals.

With only a few exceptions, the reported studies during the last six years show rather similar conclusions; that is to say, the assessed GM soybeans, rice, corn/maize and wheat would be as safe as the parental species of these plants. Therefore, based on the conclusions of the authors of these recent investigations, the use of the assessed GM plants for feed or human food should be as safe as that of their parental species. All the studies here reviewed were published in international peer-reviewed journals. Therefore, I do not question at all the results and conclusions of these investigations. However, in the same line that the authors of various recent reviews above commented, I feel that long-term studies are still clearly necessary in order to guarantee that the consumption of GM plants does not mean any health risk for the consumers. It must be noted that most recent investigations, for which no adverse/toxic effects were observed, were subchronic (90 days) studies. Notwithstanding, when long-term studies were conducted (i.e., Séralini et al., 2014b), the results were tremendously controversial.

As I also indicated in my previous articles on this subject (Domingo, 2000, 2007, 2011; Domingo and Giné Bordonaba, 2011), I disagree with the use of the "substantial equivalence" concept as a guarantee of the safety of GM plants. Why GM plants and non-GM plants, with the same nutritional capacity, should have a similar absence of health risks? This principle is not being used for any other commercial products that humans can consume. Why then should we accept it for GM plants? Finally and due to the specific policy on GMOs in Europe, I do miss long-term studies on the safety of GM plants, which that should be conducted under the auspicious of the European Union. These investigations should include long-term health effects of GM plants such as mutagenicity, teratogenicity and carcinogenicity among others.

Conflict of interest

The author declare that there are no conflicts of interest.

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