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Impact on Environment, Ecosystem, Diversity and Health from Culturing and Using GMOs as Feed and Food

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Abstract

Modern agriculture provides the potential for sustainable feeding of the world's increasing population. Up to the present moment, genetically modified (GM) products have enabled increased yields and reduced pesticide usage. Nevertheless, GM products are controversial amongst policy makers, scientists and the consumers, regarding their possible environmental, ecological, and health risks. Scientific-and-political debates can even influence legislation and prospective risk assessment procedure. Currently, the scientifically-assessed direct hazardous impacts of GM food and feed on fauna and flora are conflicting; indeed, a review of literature available data provides some evidence of GM environmental and health risks. Although the consequences of gene flow and risks to biodiversity are debatable. Risks to the environment and ecosystems can exist, such as the evolution of weed herbicide resistance during GM cultivation. A matter of high importance is to provide precise knowledge and adequate current information to regulatory agencies, governments, policy makers, researchers, and commercial GMO-releasing companies to enable them to thoroughly investigate the possible risks.

Keywords

Environmental Risk, GMO, Precision Agriculture, Toxicity, GMO Law

Abbreviations

Bt: *Bacillus thuringiensis*

Cas: CRISPER-associated

CRISPER: clustered regularly interspaced short palindromic repeats

DNA: deoxyribose nucleic acid

EFSA: European Food Safety Authority

EPSPS: enolpyruvulshikimate-3-phosphate synthase

EU: European Union

GF: gene flow

GM: genetically modified

GMO: genetically modified organism

HGT: horizontal gene flow

HR: herbicide resistance

ISAAA: International Service for the Acquisition of Agri-Biotech Applications

NAS: National Academy of Science

NOS: nopaline synthase

nptII: neomycin phosphotransferase II

US: United States

WHO: World Health Organization

1. Introduction

Genetically modified organisms (GMO) when consumed directly or after processing are rendered as genetically modified (GM) food or feed. These foods undergo artificial genetic modification during the phase of raw material production. The most common sources of raw material for GM foods are GM plants, which are genetically transformed to resist diseases, tolerate herbicides and/or insect pests. In addition, male sterility, fertility restoration, visual markers, and other metabolism related characteristics can also be influenced (Southgate et al. 1995). The estimated revenue generated by biotechnology in the United States (US) for 2012 was 323.8 billion US$, of which 128.3 billion US$ was generated from GM crops. US biotech revenue has had an observed growth of >10% over the past decade (Carlson, 2016). Similar revenue generation is expected for other countries that have adopted GM crops, as the International Service for the Acquisition of Agri-Biotech Applications (ISAAA) has reported a forecasted increase in GM crop cultivation in Asian countries (www.isaaa.org; Carlson, 2016). Global commercial cultivation of GM crops has reached to an aggregate land mass of two billion hectares over the last two decades, with total generated benefits of 150.3 billion US$ (Brooks and Barfoot, 2016). The so-called 20th anniversary (1996-2016) of GM crops resulted in significant net economic benefits (through yield and production gains as well as from cost savings) ultimately reducing yield gaps, reduced pesticide application, and conservation of zero tillage (Brookes and Barfoot, 2016; Taheri et al. 2017). However, although cultivation of GM crops and their use in food and feed has not delivered what was expected in terms of accomplishment and GM technology has attracted an ever-increasing and an extremely emotional and complex scientific and political debate, involving a very wide community of different groups ranging from environmental conservationists and ecologists, to evolutionary biologists, politicians, biotechnologists, and epidemiologists. This broader debating platform has raised certain questions, such as whether GM food and feed are safe for human and animal consumption and whether they will have harmful impacts on environment health and biodiversity. Such questions clearly need to be addressed by scientific experimentation. In an attempt to minimize such uncertainties, many laws, restrictions, and legislations have emerged, and in most countries legislative procedures for the approval of any GM crop used for food or feed now exist (Waigmann, 2012; Yaqoob et al. 2016).

The consequences of cultivating and using GM plants as food/feed can be divided into two categories. First, cultivating GM plants could have unintended impacts on ecosystem health, such as unnatural gene flow (GF), diminished genetic diversity, effects on non-target species, weediness, reduced pesticide and herbicide efficiency, herbicide and insecticide toxicity, and modification of soil and water chemistry and quality (Mertens, 2008). Similarly, cultivation of GM plants could have damaging repercussions on ecosystem complexity by diminishing biodiversity (Lovei, 2010). Second, the use of GM plants as human food and animal feed could represent a hazard to health (Suzie et al. 2008). Globally, the debate on the environmental implications of GM food and feed is still ongoing. Recent reports, including a review by Domingo (2016), the National Academy of Sciences (NAS, 2016), and the letter signed by more than one hundred Nobel laureates (http://supportprecisionagriculture.org/) in opposition to Greenpeace and in support of modern “precision agriculture”, highlight the fact that in order to feed growing populations, there is no alternative to “precision agriculture” (GM food and feed). The objective of the current updated review is to reconsider the pros and cons of GM food and feed. With reference to recent scientific reports that consider the short- and long-term risks to human and animal health, the environment, and biodiversity, we consider the arguments in support of either the Greenpeace stance or modern “precision agriculture” and biotechnologically bred foods.

2. Gene flow and its implications

The movement of gametes, individuals, or group of individuals from one location to another causes changes in gene frequency, which is referred as gene flow (GF). Among the major evolutionary forces that modify gene frequencies, GF along with selection, genetic drift, and mutation, are considered the most prominent ones. This major evolutionary force has been proceeded for millennia between cross-compatible species (Ford et al. 2006). GF, being a natural force, is not a hazard as such; rather it is the genetic contamination of recipient species that have acquired transgenes that poses risks. The movement of gametes or genes is contingent upon many factors related to environment as well as species. Apart from sexual cross-compatibility, other important factors are relevant, particularly in the case of plants, such as floral morphology, synchrony of reproductive period, and the ecology of both donor and recipient species (Lu and Snow, 2005). Given the acknowledged outcomes of this natural evolutionary force, there would appear inevitable consequences of GM cultivation, such as evolution of pathogens, pests, and superweeds, displacement/extinction of genetic diversity and species, ecological disturbance, and diminished biodiversity. Transgenes controlling unique characteristics and having strong selective advantage can escape into related cross-compatible species and could lead to modify regional as well as international trade policies in agricultural markets (Dong et al. 2016).

The possible routes of GF from GM plants to non-GM plants are pollen-mediated GF, seed-mediated GF, and vegetative propagule-mediated GF. Pollen-mediated GF has been reported at various levels in most GM crops, such as maize, rapeseed, rice, barley, cotton, and beans (Ford et al. 2006; Han et al. 2015; Yan et al. 2015). Figure 1 shows the factors affecting the frequency of

GF. Transgenes in GM plants have certain features that favor successful introgression into cross-compatible species, including dominance, location on chromosomes, and non-association with lethal alleles (Yan et al. 2015).

Transfer of the *CP4-EPSPS* (enolpyruvulshikimate-3-phosphate synthase) gene in creeping bentgrass was observed by Watrud et al. (2004). Experimental validation of transfer of the *bar* gene from cultivated rice to weedy rice was observed at the farm scale (Chen et al. 2004). Petit et al. (2007) reported adventitious contamination of P-35 S, T-NOS (nopaline synthase), MON810 (GM maize harboring the *cry1Ab*, *goxv 247*, *CP4 EPSPS*, and *nptII* genes), and T25 (GM maize containing *pat* and *bla* genes) in commercial maize seed batches. Pollen-mediated GF resulted in transfer of the NOS terminator and 35S promoter in maize land races in Mexico (Pineyro-Nelson et al. 2009). The presence of the *cry2A* gene in Basmati rice exported from Pakistan and India to the European Union (EU) could indicate the possibility of GF from GM to non-GM rice or GM contamination in seed lots (Reiting et al. 2011).Ford et al. (2015) provided evidence of biocontainment in rapeseed with the aid of field surveys, remote sensing, and agricultural statistics by considering sympatry between *Brassica rapa* and *B. oleracea.* The potential for GF is high in areas where natural counterparts or sexually cross-compatible species exist. GM × wild hybrids have been reported in almost all GM crops, including wheat, rice, soybean, corn, oilseed rape, creeping bentgrass, sugar beet, sunflower, canola, and *Arabidopsis* (Sanchez et al. 2016). The factors that affect the fitness of a developed hybrid are pleiotropy, selection, hybrid vigor, heterosis, life cycle, seed dormancy, fecundity, persistence of seeds, physiological cost of the inserted trait, genotype × environment interactions, selection pressure, frequency of successive back crossing, geography, and sympatry (Sanchez et al. 2016;Watrud et al. 2004).

Once a hybrid is generated, its fitness is the most important aspect for its persistence. Fitness is the survival of a hybrid with a good reproductive ability in a given environment (Han et al. 2015). Significant fitness differences have been observed in *B. rapa* × *B. napus*, GM sunflower × wild sunflower, GM rice × weedy rice, and sugar beet × swiss chard hybrids (Hooftman et al. 2014; Serrat et al. 2013; Mercer et al. 2006; Ellstrand 2002). Once the hybrid has passed in to the wild, its persistence as a transgenic wild weed can be a serious environmental threat, as was observed in sugar beet × swiss chard hybrids (Ellstrand 2002). Beckie and Warwick (2010) reported that transgenic oilseed rape containing the *Oxy 235* transgene can persist for years in Canada, even after the removal of GM seeds from the market. Schulze et al. (2014) reported an unexpected diversity of oilseed rape in Switzerland. The feral plants harboring GM event GT73 (GM canola containing *CP4 EPSPS*and *goxv 247* genes) were observed for two successive years (2011–2012). Similar reports from Australia have suggested that GM canola resistant to glyphosate has persistence in natural habitats outside cultivated fields (Busi and Powles, 2016). Persistence of herbicide-resistant (HR) transgenes after introgression from GM to wild soybean was observed in China. However, no significant difference in growth was found between HR soybean and its F_2 hybrids with wild soybean (Guan et al. 2015). Field experiments have revealed the relatively superior performance of F_1 hybrids as compared to weedy rice parents. These crop–weed rice F_1 [*Bacillus thuringiensis* (*Bt*) rice × weedy rice] hybrids had increased height, number of tillers, spikelets, and 1000-seed weight (Cao et al. 2009).

Horizontal gene flow (HGT) is the transfer of genes other than that via parent to offspring, either by sexual or asexual means. No direct hostile impacts have been reported as a consequence of HGT, and there are only speculated implications, such as transfer of antibiotic resistance genes and transfer of genes from GM feed to the gastrointestinal tract of animals and humans (Keese, 2008). However, transfer of the *nptII* (neomycin phosphotransferase II) gene from GM plants to soil bacteria and the detection of *Agrobacterium tumefaciens* genes in sweet potato suggest the interplay of alleles in plants and microorganisms is an established fact and cannot be neglected (Kyndt et al. 2015).

2.1. Literature survey

GF has been a topic of interest during last two decades and is a subject addressed in abundant scientific reports. We conducted a mini-survey of the literature on GF and GM plants published from 2010 to the present in the online database ISI Web of Science. Supplementary table 1 presents the surveyed literatures. We surveyed original research papers and reviews addressing this major issue and found controversial evidence that GF and the formation of hybrids is clearly an environmental threat and that this force can lead to the unwanted presence of transgenes in products that are not intended for genetic engineering. The presence of weed volunteers and ferals has been broadly addressed in these reports. The existence of such unwanted populations and transgene contamination is not only an environmental threat, but it represents additional costs for removal and management practices.

The above mentioned reports and surveyed literatures confirm that GF is a hostile natural force that can influence ecosystem health by outcrossing and transgene flow. These reports clearly indicate that the possibility of transgene introgression in wild counterparts and sexually related species is an established fact. However, the extent of the potential risks associated with GF will primarily depend upon the frequency, amount, and biological and evolutionary importance of genes. The most acceptable risk is the fitness and persistence of transgene as observed in oilseed rape in Quebec (Warwick et al. 2008). Although the interspecific hybridization of GM crop plants with their wild relatives is generally accompanied by some type of selection pressure, GF under no selection pressure is still possible because the hybrid progenies can regain the selective fitness through consecutive backcrossing. Apart from selection pressure, a genetic bridge is another important repercussion of GF with an ability to deliver transgenes to non-hybridizing plant species, as observed in a milkweed three-hybrid system in Virginia (Broyles, 2002).

The establishment of such hybrids as weeds in the same habitat or other habits is referred to as weediness, which is considered the irreversible aftereffect of HR crops. Once the hybrid gains an HR gene, its invasiveness will increase in the natural habitat and the trait will persist. Traits that can potentially increase resistance to biotic and abiotic factors and improve growth are preferred candidates. *Amaranthus palmeri* has been reported to have spread in 76 countries within a short period of 7 years. During the last four decades, chronological occurrence of HR weeds of corn, wheat, soybean, rice, and cotton has been observed (Hanson et al. 2014; www.weedcience.org, 2016). Without any selection pressure, the transfer of HR genes from cultivated to wild soybean can possibly prosper in nature (Guan et al. 2015). Concomitantly with the development of hybrids between GM plants and their sexually compatible counterparts, transfer of stacked transgene traits could be another possible consequence of GF. The major concerns regarding such GF could be transgene/host gene stability, divergence from expression, and synergistic/antagonistic effects. Apart from these main consequences, stacking of nuclear and plasmid genes and transfer of stacks of genes related to single or related pathways are also probable risks. A reduction in the expression level (34%) of stacked traits was observed in maize (*Cry* and *CP4 EPSPS* genes) when compared to the expression level of independent single events (Agapito-Tenfen et al. 2014). Stacked traits against different herbicides in oilseed rape volunteers was observed in Canada by Dietz-Pfeilstetter and Zwerger (2009). However, other studies have reported no difference in expression levels and level of control when compared to single events in maize (Raybould et al. 2012).

The aforementioned reports confirm the experimental validation of the consequences of GF as a natural force in relation to the development of GM × wild hybrids, HGT, and weediness. Although the consequences are known, when considering the incessant population growth, the yield gap of crops, and the use of GM crops in agriculture for higher production, the majority of the reported studies indicate no evidence of economic disadvantage of cultivating GM food and feed with regard to GF and possible related repercussions but it is noteworthy that weed resistance provoked by repeated use of single herbicide chemistry has caused massive economic consequences. Such a reliance on a single herbicide is considerably favoring appearance of resistant weeds. These resistant weeds are no doubt a possible way-out for gene transfer and weed × GM plant hybrids. So far, we know that gene flow is an obvious implication of GM plants and possibilities of integration of transgenes are well studies and established.

3. Ecosystem complexity and biodiversity

Although the majority of debates on the use of GM food and feed are concerned with the implications for human health, there are other effects related to the disturbance of biodiversity and creation of complexity in ecosystems, which have not been addressed in many reported studies. The scale of this issue is broad and beyond the limits of science, involving social studies and politics. It also entails a cost, similar to the environmental disturbance caused by industrial development during the last century (Suzie et al. 2008). Hence, is there any cost associated with the cultivation and use of GMOs in food and feed? To answer this many studies related to disturbance in ecosystems have been conducted and have indicated the adverse repercussions of

GM crops, particularly in relation to GF, development of resistant weeds, and altered use of herbicides and insecticides (Lovei et al. 2010).

Ecosystems are complex units of ecology that operate on vast scales and contain many food chains and complex food webs. Ecosystem services are broadly related to the production of food, feed, raw material, fertility production and maintenance, recycling of nutrients, waste management through decomposition, biological control of pests and weeds, and modification of climatic conditions. Interruption in a single unit of an ecosystem could possibly lead to the creation of complexity, diversification, destruction, and/or modification on various levels (Lovei et al. 2010). Complex interactions between and among species characterize ecosystems with high biodiversity and represent good scales at which to monitor biodiversity or ecosystem disturbance. Possible risks to ecosystem health and diversity could be the development of resistant organisms/species, unified production of traits of choice, damage to natural biocontrol agents, disturbance of soil microbial communities, reductions in pollinator populations, reduction in natural practices/processes that aid in varietal development, and rearrangement of food chains or food webs at spatiotemporal scale (Suzie et al. 2008).

Global cultivation of HR crops has led to increased use of broad-spectrum herbicides that pose serious threats to ecosystems. The main disadvantage of HR crops is the reduction of weed diversity in the agricultural landscape, which ultimately leads to a reduction in the diversity of beneficial insects (Tappeser et al. 2014). Weeds have been shown to be ecofriendly, in that they play important roles in modifying soil characteristics as well as providing habitats for beneficial farmland organism, ultimately creating complex food webs. A reduction in the weed seed bank has already been observed during the last decade by the United Kingdom Farm Scale Evaluations (Andow, 2003). Thus, it is the destruction of natural habitats that results in imbalanced food webs at the predator–prey level that ultimately leads to knock-on effects on symbiotic associations and tri-trophic interactions (Lovei et al. 2010). The increased use of insecticides is ultimately detrimental because of modifications in the foraging behavior of insects. The most important factor in this scenario will be the frequency of herbicide and pesticide use. One prominent example is the reduced emigration and excessive feeding on crickets by wolf spiders in response to glyphosate application in the western United States **(**Wrinn et al. 2012; Marchetti, 2014). A significant reduction in monarch butterfly populations has also been observed in the US and Mexico during the last decade in response to HR crop cultivation. The main reason for reductions in the populations of this butterfly is a decline in the availability of milkweed as a habitat and the main host plant for the monarch larvae (Brower et al. 2012). Reduced flowering and seeding of plants on field margins of HR oilseed rape has been linked with disturbance of the habitats of local fauna, particularly insect pollinators (Bohan et al. 2005). Reductions in bird populations (songbirds, seabirds, red kite, crow, barn owl, pheasant, gamebirds, etc.) have been reported in many countries in response to application of many insecticides and herbicides, i.e., organophosphates, carbamates, rodenticides, and alphachloralose (NAS, 2016). This raises the problematic question of whether these population reductions are attributable to the cultivation of GM crops. Whilst single herbicides are used intensively the world over and they are used in non-GM fields as well as GM fields, the consequences cannot be generalized to GM crops. Indeed, the increased application of glyphosate results in increased mortality of aquatic life on farmlands, which represents a food source for farmland birds (Isenring, 2010). Another type of shift in food webs occurs at the soil biota level, where the cultivation of HR maize and soybean resulted in increased glyphosate application, leading to higher fungal biomasses and reduced nutrient turnover (Powel et al. 2009). In contrast, in a short-term investigation, Szenasi et al. (2014)

reported no shift in the food web in response to cultivation of maize that had stacked resistance against glyphosate as well as resistance against *Coleoptera*, and *Lepidoptera*. A recent investigation conducted by Li et al. (2014) reported that cultivation of *Bt* rice (*cry1Ab*/*1Ac*or *cry2A*genes) was relatively safe to zooplankton. The report suggested that in non-*Bt* rice, the abundance of zooplankton was relatively lower (5%–20%) than that in *Bt* rice. Another report on the effects of cultivation of MON 88017 (GM maize containing *CP4 EPSPS* and *cry3Bb1* genes) on non-target organisms showed no significant differences in tri-trophic interactions, phenotypic characteristics, and composition (Devos et al. 2012). Reduction in genetic diversity and variable population frequencies of many insects and weeds have been observed as a consequence of GF (NAS, 2016). Considering the cultivation of GM crops in general and HR crops in particular, reports confirm that there is a certain pressure exerted by selective herbicides on the non-target flora and fauna of farmland, and that the long-term effects are obvious in many farmland ecosystems (Duke et al. 2012).

4. Toxicity of GM food and feed

The genetic manipulation of crop plants to enhance production is considered absolutely safe and analogous to conventional breeding. In conventional breeding non-desirable genes are also inherited by the descendants and it takes time to remove or minimize the undesirable inheritance (Keese, 2008). Creating GM organisms surmounts all types of physiological, reproductive, and natural barriers by incorporating only desirable traits (Bonny, 2016). The basic goal underlying the production of GM food and feed is to eliminate hunger and feed the ever-increasing populations by reducing the yield gap. However, Greenpeace supporters oppose such procedures and claim they are associated with health hazards. Considering the debates surrounding the repercussions of GM food and feed, the scientific community is under pressure to conclusively determine whether it is safe to consume such food. In an attempt to resolve this issue, many research groups have recently used GM as a food and feed on different experimental organisms.

The results of some studies have unexpectedly indicated that there are potential health hazards (Pusztai et al. 1996; Seralini et al. 2012, 2014). Since 1998, two famous studies have been subjected to severe criticism from scientists, societies, the media, and politicians, namely, the

Pusztai affair and the Seralini affair (Information box. 1).

Information box 1.

Pusztai affair (1998) and Seralini affair (2012)

The first controversy started when Arpad Pusztai revealed his unpublished results of thickening of gut mucosa in response to GM potato harboring GNA (*Galanthus nivalis agglutinin*). He conducted twelve experiments and reported statistically significant differences in gut mucosa thickening, however, in an explanation he reported that there were some differences in protein level (20%) as well as sugar and starch contents, which lead to discontinuation of the experiment. The crypt length of two experimental groups of rats i.e. rats fed with raw modified GM potato and non-GM potato, were significantly different. The third group of rats fed with cooked potato did not show significant differences from the control which lead to generation of results that the only reason for thickening of gut mucosa was the transformation procedure. However, his coworkers suggested the CMV promotor may be responsible for the results. There was huge public, media, political and industrial pressure on the authors as well as the institute which lead towards suspension of the scientist. Later the work undergone through an audit by Rowett Institute and peer review by Royal Society which ended up with the comments that the experiments were poorly conducted having many uncertainties and lacked appropriate statistical methods and models. However, the data was published as a letter in *The Lancet* in 1999 with the concluding remarks that no significant difference were observed in treated and control rats, although it has been heavily criticized to this day(Pusztai, 1996).

Fourteen years after the first controversy, an article reporting increased tumor size in rats fed with GM maize and roundup was published in *Food and Chemical Toxicology* by French molecular biologist Gilles-Eric Seralini. As soon as the report was published, it faced criticism from the scientific community and public, resulting in retraction of the article. The authors did not agree with retraction and arranged press conference where they released a book and documentary video in support of their research. The most significant criticism was that the frequency of tumor appearing was higher in the strain of rats used in the study. Many institutes including King’s College London, Washington Post, New York University, University of Calgary, Canadian regulatory agencies, National Agency for Food Safety France, Technical University of Denmark contended that the experiments were in adequately conducted and reported the work was republished in Environmental Sciences Europe in 2014 with positive comments, although it remains controversial (Seralini et al. 2012, 2014).

Whilst neither study categorically stated that GM food and feed is unsafe, it is clear that further evaluation is necessary to inform further legislation and testing prior to approval for public consumption.

The issue of GM food and feed toxicity has always been controversial and the evidence that has accumulated thus far does not indicate a need to impose any direct restrictions on the use of GM food. Recent research on the health hazards of GM food and feed is summarized in Table 1. The main concern is the necessity to examine the consequences of transferred gene and the potential toxicity of expressed proteins. GM rice, soybean, maize, and wheat, alone or in combination, have been fed to rats, broiler chickens, layer hens, dairy cows, monkeys, frogs, and pigs. Most of the studies conducted lasted for up to 90 days and recorded pathological, hematological, histopathological, serum chemistry, macroscopic, food intake, and reproduction-related characteristics (Tyshko et al. 2014, Tyshko and Sadykova, 2016). In all the studies, only minor or no adverse changes were recorded and the general conclusions were that GM food and feed have no hazardous effects compared with non-GM diets. Although the reports do not indicate direct risks to human and animal health, when the details of all the reports are considered, certain effects were observed, such as statistically significant differences in clinical performance of SD rats in response to consumption of high amylose and resistant GM-rice (Zhou et al. 2011). Song et al. (2015) concluded that biochemical and hematological blood parameters were comparable when SD rats were fed with *Bt* transgenic rice (expressing *cry1Ab*). Broiler chickens fed with GM soybean (expressing an imidazolinone tolerance gene) had lower body weight in comparison to the controls. Since their commercialization, GM foods have been consumed by millions of people across the globe and to date no toxicity has been reported scientifically, clinically, or legally (Domingo, 2016; Suzie et al. 2008). A recent three generation reproduction toxicity study on SD rats fed with GM rice containing cry1Ac and sck genes clearly mentioned several minor differences in blood chemistry parameters. The controversies related to the use of GM food and its potential risks to human health have mostly been confused with the allergenic action of some plants. Furthermore, it could be suggested that interpretation of the various studies has been somewhat selective by certain international organizations.

Apart from mice, rats, pigs, and chickens, many researchers have conducted studies to investigate the effects of GM crop cultivation on the health of a range of other organisms. In this regard, the most famous study was that conducted by Losey et al. (1999), who reported the mortality of Monarch butterfly larvae that were affected by *Bt* maize pollen. However, subsequent investigations on the same species reported negligible or no such evidence (Sears et al. 2001; Dively et al. 2004). Other studies, which have investigated the effects on many herbivores, lacewings, honeybees, and earth worms, have reported contradictory results. For example, Hendriksma et al. (2011) reported toxicity of *Heliconia rostrata* pollen to honey bees, whereas GM maize pollen was found to be nontoxic. Feeding Dekalb 818 to *Daphnia manga* resulted in reduced egg production (Szenasi et al. 2014). Yaqoob et al. (2016) and Domingo (2016) reviewed recent reports on rodents, pigs, poultry, frogs, and non-target insect and herbivore species, and concluded that GM cultivation is rather safe and that GM crops perform similarly to non-GM crops with a relatively higher production. A recent report on transcriptomics and metabolomics analysis in an established rat toxicity model system, where rats were fed with NK603 and its counterpart, did not arrive any conclusion regarding pathologies and toxicities (Mesnage et al. 2017). However, when the detailed experimental results of all reviewed reports are considered, certain minor toxic effects can be observed suggesting that there are some health implications such as non-alcoholic fatty acid liver disease and presence of associated with consumption of GM crops. Whatever the case, the toxic effects of GM food consumption could be seen in a few reports even though the authors of those reports call for further specific and independent research for each characteristic risk.

A recent report from NAS (2016) revealed that cultivation of GM crops has had no negative impact on the environment, ecosystems, biodiversity, or health. By growing herbicide- and insect-resistant crops, the amount of pesticide and herbicide has been decreased, whereas yield has been increased. However, the report did highlight concerns regarding the changes in the presence and concentrations of secondary metabolites made through genetic engineering as well as conventional breeding. Furthermore, the report clearly states that "the current animal-testing protocols based on OECD guidelines for the testing of chemicals use small samples and have limited statistical power; therefore they may not detect existing differences between GM and non-GM crops or may produce statistically significant results that are not biologically meaningful". The report further found that statistically significant differences are there between GM and non-GM plants regarding chemical composition and nutrients. These nutritional changes accompanied with transcriptomics and proteomics variations may possibly attributed to genetics and environment.

It is clear that the issue regarding toxicity of GM food and feed is not over and a consensus has not appeared (Hilbeck et al. 2015). The current range of toxicity tests present many limitations such as limited period of exposure and are strictly case specific (Tsatsakis et al. 2017a; NAS, 2016). It is also important to bear in mind that humans are exposed to a complex mixture of GM diets rather one single event. In such a situation, the current range of testing should be sufficiently criticized. The current approaches in testing endocrine EDCs lack the ability to simulate the real-world exposure scenarios of exposure to mixtures of compounds with endocrine disruptor properties that could lead to synergic or potentiation effects, even at low concentrations of exposures (Hernandez et al., 2013; Hernandez and Tsatsakis, 2017). Whilst international regulatory organizations have increased their interest in combined exposure and mixture testing this focus so far has been on commercial chemical mixtures with similar mechanisms of action (EFSA, 2013a; EFSA, 2013b; US-EPA, 2006). It has been recognized from toxicological perspectives, that new experimental approaches are necessary for mixture testing that can address the key questions related to health concerns after long term low- dose real-world exposure to non-commercial artificial mixtures (Tsatsakis et al., 2016; Tsatsakis and Lash, 2017; Tsatsakis et al., 2017c).

A new promising animal protocol has already been proposed for evaluating the cumulative toxicity of different chemical mixtures by using realistic doses following long term exposure (Docea et al., 2016; Tsatsakis et al., 2017b). This experimental approach has a potential to change the regulatory approach in assessing the toxicity of various agents in the chemical and food industry in order to avoid potentiation of toxicity. It is important to conduct toxicological studies which focus on the simultaneous investigation of several key endpoints like target organ toxicity (cardiotoxicity and neurotoxicity especially) and also non-target direct toxicity such as oxidative stress, endocrine disruption and genotoxicity. Such a approach would be easily adapted towards toxicity evaluation of GM food and feed.

5. Other unintended implications

Precision agriculture is associated with certain modifications to agricultural practices which can change local fauna and flora. Whilst the cultivation of GM crops has many unintended harmful effects on the environment, soil, water, and efficiency of insect, pest, and weed control, it is also clear that HR crops encourage the use of broad-spectrum herbicides with higher intensities. These increased dosages lead to higher concentrations of herbicides in farmland soil and water, thus impacting flora and fauna of farmland (Duke et al. 2012). Development of resistance against insecticides and herbicides has been observed as an indirect and unintended effect of GM crop cultivation. This so-called selective pressure of broad-spectrum herbicides, along with many evolutionary events, has resulted in the development of herbicide resistance in horseweed, Asiatic dayflower, wild buckwheat, annual ryegrass, western corn rootworm, and common lambs quarters (Bonny, 2016). Similarly, development of resistance has also been observed in the diamondback moth in response to cultivation of *Bt* crops in many countries (Tabashnik, 2015; Gassmann et al. 2011). The mechanisms underlying the evolution of such resistance depends upon species, mating behavior, ecosystem micro- and macro-climate, transgene expression level, frequency of insecticide or herbicide application, and mode of action of the applied chemical. Shifts in weed populations due to higher usage of herbicides has also been reported in many parts of the world. Common water hemp, velvetleaf, hemp sesbania, horseweed, nightshade, nuts edge, ivy leaf morning glory, and shatter cane have been reported to survive under the selective pressure of glyphosate **(**Yaqoob et al. 2016; Mertens, 2008). These reports emphasize that repeated and increased application of broad-spectrum herbicides will result in shifts in weed populations from high sensitivity to reduced sensitivity and the evolution of herbicide tolerance. Another important possible risk of GM crop cultivation is the addition of naked DNA to the environment. However, the risk should be seen in the context of the tons of DNA that already enter ecosystems in the form of compost, manures, decomposed fruits, decaying plants, leaves, and pollen (Heinemann et al. 2013). Selective pressure has lead towards development of resistance in many weeds and it must be considered as a long term impact of GM plants and must be investigated on a broader scale.

6. Global Political Stance

Prior to commercial cultivation and end-user consumption of GM crops, food and feed must pass through a rigorous regulatory and legislative procedure to receive authorization for public and environmental safety. The regulatory procedures are mainly based on the availability of objective-oriented data received from independent scientific investigations. These regulations and laws were essentially drawn up to address the direct and indirect risks associated with the cultivation of GM crops. The primary assessment of GM crops is based on their agronomic traits, nutrient composition, repository of toxins, and anti-nutrients (Bartholomaeus et al. 2013). During the last decade, GMO crops were commercially cultivated in 28 countries; however, the requirements for regulation policies differ in different countries and even within regulatory agencies (Yaqoob et al. 2016).

However, all regulatory commissions have attempted to define GM risk assessment in an essentially similar manner, i.e. identification, characterization, and assessment of hazards, and, finally, characterization of risk. On one side, the US approach to the regulation of GMOs is primarily contingent upon the nature of the product rather than the process applied for the development of the product. Absence of any federal legislation in the US led to the handling and assessing of GMOs by several regulatory organisations, such as the Animal and Plant Health Inspection Service, Food and Drug Administration and Environment Protection Agency (www.loc.gov). In contrast to the US, the EU has a totally different focus, i.e., the process instead of the product. In the EU all the regulatory actions are carried out by the European Food Safety Authority (EFSA). The EFSA has a strict policy regarding the labeling of GM materials, whereas the US legislative agencies are not that much strict. Overall, the number of GM crops approved in the US is higher than in that in the EU, and individual case approval in the US is relatively easier and faster than in the EU (Lau, 2015). The World Health Organization (WHO) in association with the Food and Agriculture Organization (FAO) has published the Codex Guidelines on safety assessment of GM foods. The WHO's stance regarding GMO assessment is that "At present, there is no definitive test that can be relied upon to predict allergic responses in humans to a newly expressed protein" and concludes by stating that case-by-case assessment is mandatory (WHO, 2016, www.who.int/en/). The principle of "substantial equivalence" in the US and WHO assessment procedure is quite similar to the EFSA's principle of "comparative assessment." Both principles refer to the conventional counterpart and more particularly its history (www.efsa.europa.eu; www.fda.gov; WHO, 2016). However, these principles have received severe criticism, mainly because they take into consideration chemical similarity rather than other more relevant data of immunological, toxicological, and biological origin. A recent study on NK603 Roundup-tolerant GM maize based on multi-omics analysis showed that GM and its counterpart are not substantially equivalent. The study confirmed that there was imbalance in energy metabolism, oxidative stress, and polyamines content (Mesnage et al. 2016). A list of regulatory agencies and their available regulatory guidance is presented in Table 2. Additionally, details of the eight countries with the largest areas under GM cultivation 2011-2015 are summarized in Figure 2; whilst these data suggest that the total area of GM crops is increasing, the process of risk assessment adopted by the regulatory authorities is improving with time, albeit with shortcomings and uncertainties. These problems involve the duration of long-term and short-term assessments, dose-response curves, level of exposure in natural versus laboratory conditions, and sets of controls used in the examinations (Waigmann, 2012). The "coordinated framework" of the US for regulation of GMOs have undergone various reforms but still seems to be largely unchanged (Benbrook, 2016). Furthermore, the principle of substantial equivalence does not necessarily or completely compare a GMO with its conventional counterpart. The comparison must include dose levels, toxicity levels, and environmental conditions. Moreover, in organizing comparisons between GM and non-GM organisms, it is rather difficult to decide on the appropriate conventional counterpart. The anti-nutritional factors present in so-called conventional counterparts and other non-economical characteristics can be a problem in the comparison process. The increasing uncertainties that have emerged in response to many ill-conducted studies and controversial data have caused doubts among those who are using GM foods. Such doubts can possibly be allayed by thorough legislation and a comprehensive assessment procedure by authorized scientific platforms.

7. Future of GM Food and Feed

In the intermediate future, GM foods and feeds will prosper in the Asian and African countries, as is evident from the growth of these product during the last 5 years (Figure 2; ISAAA 2015). However, the mature GM crop markets, such as those in the US, Brazil, and the EU have little scope for expansion. In the near future, it is expected that there will be more releases of GM crops with stacked traits carrying multiple stress tolerance genes, given that in the 2015 ISAAA brief there is mention of 85 GM products in the pipeline. The applications of more precise, rapid, and well-regulated technologies, such as CRISPR (clustered regularly interspaced short palindromic repeats), CRISPR-associated (Cas) genes, and new breeding technologies, will increase in usage as these technologies come under proportionate legislation with an advantage of being science-based and appropriate for the purpose. Regarding safety assessment and health hazards, there will be a need for more precise, animal-specific, organ-specific, and long-term assessment procedures, with special consideration given to novel toxins, dose, potentially toxic mixtures and the combined effect of stacked traits on metabolism and other body mechanisms.

8. Conclusion

Collectively, the studies cited in this review clearly indicate that GM crops are prospering and have the potential to spread across the globe. The studies mention no direct harm to either human or animal health as a consequence of the consumption of GM food or feed. However, there remain concerns regarding the long-term usage of GM food and feed. Evidence presented indicating damage to the environment and biodiversity gives considerable grounds for concern, particularly with regard to the consequences of gene flow. Development of resistance against broad-spectrum herbicides and insecticides are undeniable consequences associated with the cultivation of GM crops. The complexity of food webs and food chains in farm ecosystems has, however, made assessment of the precise effects problematic and thus it will be essential to conduct further long-term in-field trials. It is also clearly necessary to focus the attention of policy makers, regulatory authorities, governments, and GM-releasing companies on the need to examine and authenticate the possible long term unexplored effects, risks and damages to ecosystems, biodiversity, and health prior to the release of any GM food or feed. Labeling should be mandatory and should be considered as a basic consumer right.

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References

Agapito-Tenfen, S. Z., Vilperte, V., Benevenuto, R.F., Rover, C.M., Traavik, T.I., Nodari, R.O., 2014. Effect of stacking insecticidal cry and herbicide tolerance epsps transgenes on transgenic maize proteome. BMC Plant Biol. 4, 346.

Andow D.A., 2003. UK farm-scale evaluations of transgenic herbicide-tolerant crops. Nature Biotech. 21, 1453-1454. http://doi:10.1038/nbt1203-1453.

Arjo, G., Capell T., Matias-Guiu, X., Zhu, C.F., Christou, P., Pinol C., 2012. Mice fed on a diet enriched with genetically engineered multivitamin corn show no sub-acute toxic effects and no sub-chronic toxicity. Plant Biotechnol. J. 10:1026-1034.

Bartholomaeus, A., Parrott, W, Bondy, G., Walker, K., & on behalf of the ILSI International Food Biotechnology Committee Task Force on the Use of Mammalian Toxicology Studies in the Safety Assessment of GM Foods. 2013. The use of whole food animal studies in the safety assessment of genetically modified crops: Limitations and recommendations. Critical Reviews Toxicol. 43, 1-24. DOI: 10.3109/10408444.2013.842955.

Beckie, H.J., Warwick, S.I., 2010. Persistence of an oilseed rape transgene in the environment. Crop Prot. 29, 509–512.

Benbrook, C., 2016. Enhancements needed in GE crop and food regulation in the U.S. Front. Pub. Health. 4, doi: 10.3389/fpubh.2016.00059.

Bohan, D.A., Boffey, C.W.H., Brooks, D.R., Clark, S.J., Dewar, A.M., Firbank, L.G., Haughton, A.J., Hawes, C., Heard, M.S., May, M.J., Osborne, J.L., Perry, J.N., Rothery, P., Roy, D.B., Scott, R.J., Squire, G.R., Woiwod, I.P., Champion, G.T., 2005. Effects on weed and invertebrate abundance and diversity of herbicide management in genetically modified herbicide- tolerant winter-sown oilseed rape. Proc. R. Soc. B. 272, 463-474.

Bonny, S., 2016. Genetically Modified Herbicide-Tolerant Crops, Weeds, and Herbicides: Overview and Impact. Environ. Manage. 57, 31-48. http://doi: 10.1007/s00267-015-0589-7.

Brookes, G., Barfoot, P., 2016. Global income and production impacts of using GM crop technology 1996-2015. GM Crop. Food. 7, 38-77.

Brouk, M.J., Cvetkovic, B., Rice, D.W., et al. 2011. Performance of lactating dairy cows fed corn as whole plant silage and grain produced from genetically modified corn containing event DAS-59122–7 compared to a nontransgenic, near-isogenic control. J. Dairy Sci. 94, 1961-6.

Brower, L.P., Taylor, O.R., Williams, E.H., Slayback, D.A., Zubieta, R.R., Ramirez, M.I., 2012. Decline of monarch butterflies overwintering in Mexico: is the migratory phenomenon at risk? Insect Conservation and Diversity 5,95-100.

Broyles, S.B., 2002. Hybrid bridges to gene flow: a case study in milkweeds (Asclepias). Evolution. 56, 1943-53.

Busi, R., Powles, S.B., 2016. Transgenic glyphosate-resistant canola (*Brassica napus*) can persist outside agricultural fields in Australia. Agri. Ecosystems Environ. 220, 28-34.

Carlson, R., 2016. Estimating the biotech sector’s contribution to the US economy. Nature Biotechnology. 34, 247-255.

Cao, Q.J., Xia, H., Yang. X., Lu, B.R., 2009. Performance of hybrids between weedy rice and insect-resistant transgenic rice under field experiments: implication for environmental biosafety assessment. J. Integr. Plant Biol. 51, 1138-48. doi: 10.1111/j.1744-7909.2009.00877.x.

Cao, S.S., Xu, W.T., Luo, Y.B., He, X.Y., Yuan, Y.F., Ran, W.J., Liang, L.X., Huang, K.L., 2011. Metabonomics study of transgenic *Bacillus thuringiensis* rice (T2A-1) meal in a 90-day dietary toxicity study in rats. Mol. Bio. Syst. 7, 2304-2310.

Chen, L., Sun, Z., Liu, Q., Zhong, R., Tan, S., Yang, X., Zhang, H., 2016. Long-term toxicity study on genetically modified corn with cry1Ac gene in a Wuzhishan miniature pig model. Sci. Food Agric. 96, 4207-14. doi: 10.1002/jsfa.7624.

Chen, L.J., Lee, D.S., Song, Z.P., Suh, H.S., Lu, B., 2004. Gene Flow from Cultivated Rice (*Oryza sativa*) to its Weedy and Wild Relatives. Annal. Bot. 93, 67-73.

Chen, X., Wang, J., Zhu, H., Li, Y., Ding, J., Peng, Y., 2015. Effects of transgenic cry1Ca rice on the development of *Xenopus laevis*. PLoS One. 10, e0145412.

Chukwudebe, A., Privalle, L., Reed, A., Wandelt, C., Contri, D., Dammann, M., Groeters, S., Kaspers, U., Strauss, V., Van,Ravenzwaay, B., 2012. Health and nutritional status of Wistar rats following subchronic exposure to CV127 soybeans. Food Chem. Toxicol. 50, 956-971.

Delaney, B., Karaman, S., Roper, J., Hoban, D., Sykes, G., Mukerji. P., Frame, S.R., 2013. Thirteen week rodent feeding study with grain from molecular stacked trait lepidopteran and coleopteran protected (DP-ØØ4114-3) maize. Food Chem. Toxicol. 53, 417-427.

Delaney, B., Appenzeller, L.M., Roper, J.M., Mukerji, P., Hoban, D., Sykes, G.P., 2014. Thirteen week rodent feeding study with processed fractions from herbicide tolerant (DP-073496-4) canola. Food Chem. Toxicol. 66, 173-184.

Devos, Y., De Schrijver, A., De Clercq, P., Kiss, J., Romeis, J., 2012. *Bt*-maize event MON 88017 expressing Cry3Bb1 does not cause harm to non-target organisms. Transgenic Res. 21, 1191-214. doi: 10.1007/s11248-012-9617-z.

Dietz-Pfeilstetter, J., Zwerger, P., 2009. In-field frequencies and characteristics of oilseed rape with double herbicide resistance. Environ. Biosafety Res. 8, 101-111. http://doi:10.1051/ebr/2009006.

Domingo, J.L., 2016. Safety assessment of GM plants: An updated review of the scientific literature. Food Chem. Toxicol. doi: 10.1016/j.fct.2016.06.013.

Dong, S., Liu, L., Yu, C., Zhang, Z., Chen, M., Wang, C., 2016. Investigating Pollen and Gene Flow of WYMV-Resistant Transgenic Wheat N12-1 Using a Dwarf Male-Sterile Line as the Pollen Receptor. PLoS One. 11, e0151373. doi: 10.1371/journal.pone.0151373.

Dively, G.P., Rose, R., Sears, M.K., Hellmich, R.L., Stanley-Horn, D.E., Calvin, D.D., Russo, J.M., Anderson, P.L., 2004. Effects on monarch butterfly larvae (Lepidoptera: Danaidae) after continuous exposure to Cry1Ab-expression corn during anthesis. *Environ. Entomol.* 33, 1116-1125. http://dx.doi.org/10.1603/0046-225X-33.4.1116.

Duke, S.O., Lydon, J., Koskinen, W.C., Moorman, T.B., Chaney, R.L., Hammerschmidt, R., 2012. Glyphosate Effects on Plant Mineral Nutrition, Crop Rhizosphere Microbiota, and Plant Disease in Glyphosate-Resistant. Crops. J. Agric. Food Chem. 60, 10375-10397. http://dx.doi.org/10.1021/jf302436u.

EFSA (European Food Safety Authority). 2013a. International Framework Dealing with Human Risk Assessment of Combined Exposure to Multiple Chemicals. EFSA. J. 11, 7. 3313.

EFSA (European Food Safety Authority). 2013b. Scientific opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile. EFSA. J. 11, 3293.

Ellstrand, N.C., 2002. Gene flow from transgenic crops to wild relatives: what have we learned, what do we know, what do we need to know? In: Scientific methods workshop: Ecological and agronomic consequences of gene flow from transgenic crops to wild relatives. Meeting proceedings, 39-46.http://www.biosci.ohio-state.edu/~lspencer/gene_flow.htm.

Fang, J., Feng, Y., Zhi, Y., Zhang, L., Yu, Z., J, X., 2017. A 90-day toxicity study of GmTMT transgenic maize in Sprague-Dawley rats. Regultory Toxicol. Pharmacol. 85, 48-54.

Ford, C.S., Allainguillaume, J., Fu, T.R., Mitchley, J., Wilkinson, M.J., 2015. Assessing the value of imperfect biocontainment nationally: rapeseed in the United Kingdom as an exemplar. New Phytologist. 205, 1342-1349.

Ford, C.S., Allainguillaume, J., Grilli-Chantler, P., Cuccato, J., Allender, C.J., Wilkinson, M.J., 2006. Spontaneous gene flow from rapeseed (*Brassica napus*) to wild*Brassica oleracea*. Proc. Biol. Sci. 273, 3111-3115. doi: 10.1098/rspb.2006.3686.

Gassmann, A.J., Petzold-Maxwell, J.L., Keweshan, R.S., Dunbar, M.W., 2011. Field-Evolved Resistance to *Bt* Maize by Western Corn Rootworm. PLoS One. 6, e22629. doi:10.1371/journal.pone.0022629.

Guan, Z.J., Zhang, P.F., Wei, W., Mi, X.C., Kang, D.M., Liu, B., 2015. Performance of hybrid progeny formed between genetically modified herbicide-tolerant soybean and its wild ancestor. AoB PLANTS 7, plv121. doi:10.1093/aobpla/plv121.

Guo, Q.Y., He, L.X., Zhu, H., Shang, J.L., Zhu, L.Y., Wang, J.B., Li, Y., 2015. Effects of 90-day feeding of transgenic maize *BT*799 on the reproductive system in male Wistar rats. Int. J. Environ. Res. Public Health. 12, 15309-15320.

Han, S., Zou, S., He, X., Huang, K., Mei, X., 2016. Potential subchronic food safety of the stacked trait transgenic maize GH5112E-117C in Sprague-Dawley rats. Transgenic Res. 25, 453-63. doi: 10.1007/s11248-016-9944-6.

Han, S.M., Lee, B., Won, O.J., Hwang, K.S., Suh, S.J., Kim, C., Park, K.W., 2015. Gene flow from herbicide resistant genetically modified rice to conventional rice (*Oryza sativa* L.) cultivars. J. Ecol. Environ. 38, 397-403.

Hanson, B.D., Fischer, A.J., McHughen, A., Jasieniuk, M., Shrestha, A., Jhala, A.J., 2014. Herbicide resistant weeds and crops, in: Fennimore, S.A., Bell, C. (Eds.), Principle of weed science. California Weed Science Society.

Hardisty, J.F., Banas, D.A., Gopinath, C., Hall, W.C., Hard, G.C., Takahashi, M., 2013. Spontaneous renal tumors in two rats from a thirteen week rodent feeding study with grain from molecular stacked trait lepidopteran and coleopteran resistant (DP-ØØ4114-3) maize. Food Chem. Toxicol. 53, 428-431.

He, X., de Brum, P.A., Chukwudebe, A., Privalle, L., Reed, A., Wang, Y., Zhou, C., Wang, C., Lu, J., Huang, K., Contri, D., Nakatani, A., de Avila, V.S., Klein, C.H., de Lima, G.J., Lipscomb, E.A., 2016. Rat and poultry feeding studies with soybean meal produced from imidazolinonetolerant (CV127) soybeans. Food Chem. Toxicol. 88, 48-56.

Heinemann, J.A., Agapito-Tenfen, S.Z., Carman, J.A., 2013. A comparative evaluation of the regulation of GM crops or products containing dsRNA and suggested improvements to risk assessments. Environ. Int. 55, 43-55.

Hendriksma, H.P., Hartel, S., Steffan-Dewenter, I., Testing Pollen of Single and Stacked Insect-Resistant *Bt*-Maize on In vitro Reared Honey Bee Larvae. PLoS ONE 6, e28174. http://doi:10.1371/journal.pone.0028174.

Herman, R.A., Dunville, C.M., Juberg, D.R., et al. 2011a. Performance of broiler chickens fed diets containing DAS-68416–4 soybean meal. GM Crops. 2, 169-75.

Herman, R.A., Dunville, C.M., Juberg, D.R., et al. 2011b. Performance of broiler chickens fed event DAS-40278–9 maize containing the aryloxyalkanoate dioxygenase-1 protein. Regul. Toxicol. Pharmacol. 60, 296-9.

Hernandez, A.F., Parron, T., Tsatsakis, A.M., Requena, M., Alarcon, R., Lopez-Guarnido, O. 2013. Toxic effects of pesticide mixtures at a molecular level: Their relevance to human health. Toxicol. 307, 136-145.

Hernandez, A.F., Tsatsakis, A.M. 2017. Human exposure to chemical mixtures: challenges for the integration of toxicology with epidemiology data in risk assessment. Food Chem. Toxicol. 103, 188-193. doi: 10.1016/j.fct.2017.03.012.

Hilbeck, A., Binimelis, R., Defarge, N., Steinbrecher, R., Szekacs, A., Wickson, f., Michael, A., Bereano, P.L., Clark, E.A., Hansen, M., Novotny, E., Heinemann, J., Meyer, H., Shiva, V., Wynne, B., 2015. No scientific consensus on GMO safety. Env. Sci. Europe. 27. DOI: 10.1186/s12302-014-0034-1.

Hooftman, D.A.P., Bullock, J.M., Morley, K., Lamb, C., Hodgson, D.J., Bell, P., Thomas, J., Hails, R.S., 2014. Seed bank dynamics govern persistence of Brassica hybrids in crop and natural habitats. Ann. Bot. 1-11. doi:10.1093/aob/mcu213

Hu, Y., Zhuo, Q., Gong, Z., Piao, J., Yang, X., 2017. Three-generation reproduction toxicity study of genetically modified rice with insect resistance genes. Food Chem. Toxicol. 99, 190-198. doi: 10.1016/j.fct.2016.11.025.

Ibrahim, M.A.A., Okasha, E.F., 2016. Effect of genetically modified corn on the jejunal mucosa of adult male albion rats. Exp. Toxicol. Pathol. 68, 579-588.

Isenring, R., 2010. Pesticides and the loss of biodiversity. Pesticide Action Network, Europe. Development House 56-64 Leonard Street London EC2A 4LT. http://www.pan-europe.info/old/Resources/Briefings/Pesticides_and_the_loss_of_biodiversity

International Service for the Acquisition of Agri-Biotech Applications-Brief 51-2015: Executive Summary. 2015. http://isaaa.org/resources/publications/briefs/51/executivesummary/default.asp

Keese, P., 2008. Risks from GMOs due to Horizontal Gene Transfer. Environ. Biosafety Res. 7, 123-149.

Kyndt, T., Quispe, D., Zhai, H., Jarret, R., Ghislain, M., Liu, Q., Gheysen, G., Kreuze, J.F., 2015. The genome of cultivated sweet potato contains Agrobacterium T-DNAs with expressed genes: An example of a naturally transgenic food crop. Proc. Natl. Acad. Sci. U.S.A. 112, 5844-5849.

Lau, J., 2015. Same science, different policies: Regulating Genetically Modified Foods in the U.S. and Europe. Science in the news. Harvard University. http://sitn.hms.harvard.edu/flash/2015/same-science-different-policies/

Li, G., Wang, Y., Liu, B., Zhang, G., 2014. Transgenic *Bacillus thuringiensis* (*Bt*) Rice Is Safer to Aquatic Ecosystems than Its Non-Transgenic Counterpart. PLoS ONE. 9, e104270. doi:10.1371/journal.pone.0104270.

Li, Z., Gao, Y., Zhang, M., Feng, J., Xiong, Y., 2015. Effects of a diet containing genetically modified rice expressing the Cry1Ab/1Ac protein (*Bacillus thuringiensis* toxin) on broiler chickens. Arch. Anim. Nutr. 69, 487-498.

Liang, C.L., Li, Y.N., Zhang, X.P., Song, Y., Wang, W., Fang, J., Cui, W.M., Jia, X,D., 2012. Immunotoxicologic assessment of genetically modified drought-resistant wheat T349 with GmDREB1. Zhonghua Yu Fang Yi Xue Za Zhi. 46, 556-560 (in Chinese).

Liang, C.L., Zhang, X.P., Song, Y., Jia, X.D., 2013. Immunotoxicological evaluation of wheat genetically modified with TaDREB4 gene on BALB/c mice. Biomed. Enviro. Sci. 26, 663-670.

Liu, P., He, X., Chen, D., Luo, Y., Cao, S., Song, H., Liu, T., Huang, K., Xu, W., 2012. A 90-day subchronic feeding study of genetically modified maize expressing Cry1Ac-M protein in Sprague-Dawley rats. Food Chem. Toxicol. 50, 3215-3221.

Losey, J,E., Rayor, LS, Carter ME.1999. Transgenic pollen harms monarch larvae. Nature, 399, 214.

Lovei, G.L., Bøhn, T., Hilbeck, A, 2010. Biodiversity, Ecosystem Services and Genetically Modified Organisms. Third World Network, 131 Macalister Road 10400 Penang, Malaysia. ISBN: 978-967-5412-13-4.

Lu, B., Snow., A., 2005. Gene Flow from Genetically Modified Rice and Its Environmental Consequences. BioScience. 55, 669-678.

Marchetti, M.F., 2014. The Effects of a Glyphosate-Based Herbicide (Roundup®) and temperature on the Foraging of the Wolf Spider *Pardosa milvina* (Araneae: Lycosidae). Master thesis. Department of Zoology. Faculty of Miami University.

Mao, J., Sun, X., Cheng, J.H., Shi, Y.J., Wang, X.Z., Qin, J.J., Sang, Z.H., He, K., Xia, Q., 2016. A 52-week safety study in *Cynomolgus macaques* for genetically modified rice expressing Cry1Ab/1Ac protein. Food Chem. Toxicol. 95, 1-11. http://dx.doi.org/10.1016/j.fct.2016.06.015.

McNaughton, J., Roberts, M., Rice, D., et al. 2011a. Comparison of broiler performance and carcass yields when fed transgenic maize grain containing event DP-O9814O-6 and processed fractions from transgenic soybeans containing event DP-356O43–5. Poult. Sci. 90, 1701-11.

McNaughton, J., Roberts, M., Rice, D., et al. 2011b. Nutritional equivalency evaluation of transgenic maize grain from event DPO9814O-6 and transgenic soybeans containing event DP-356O43–5: laying hen performance and egg quality measures. Poult. Sci. 90, 377-89.

Mercer, K.L., Andow, D.A., Wyse, D.L., Shaw, R.G., 2007. Stress and domestication traits increase the relative fitness of crop–wild hybrids in sunflower. Ecol. Lett. 10, 383-393. doi:10.1111/j.1461-0248.2007.01029.x.

Mertens, M., 2008. Assessment of Environmental Impacts of Genetically Modified Plants. BfN - Skripten 217. Federal Agency for Nature Conservation. New York, USA.

Mesnage, R., Arno, M., Seralini, G.E., Antoniou, M.N., 2017. Transcriptome and metabolome analysis of liver and kidneys of rats chronically fed NK603 Roundup-tolerant genetically modified maize. Environ. Sci. Eur. 29. doi: 10.1186/s12302-017-0105-1.

Mesnage, R., Agapito-tenfen, SZ., Vilperte, V., Renney, G., Ward, M., Seralini, G.E., Nodari, R.O., Antoniou, M.N., 2016. An integrated multi-omics analysis of the NK603 Roundup-tolerant GM maize reveals metabolism disturbances caused by the transformation process. Sci. Report. 6, 37855. Doi:10.1038/srep37855.

National Academy of Sciences. 2016. Genetically Engineered Crops: Experiences and Prospects. The National Academies Press, 500 Fifth Street NW Washington, DC 20001.

Petit, L., Pagny, G., Baraige, F., Nignol, A., Zhang, D., Fach, P., 2007. Characterization of Genetically Modified Maize in Weakly Contaminated Seed Batches and Identification of the Origin of the Adventitious Contamination. J. AOAC Int., 90, 1098-1106.

Petrick, J.S., Frierdich, G.E., Carleton, S.M., Kessenich, C.R., Silvanovich, A., Zhang, Y., Koch, M.S., 2016. Regulatory Toxicol. Pharmacol. 81, 57-68. http://dx.doi.org/10.1016/j.yrtph.2016.07.009.

Pineyro-Nelson, A., Heerwaarden, J.V., Perales, H.R., Serratoshernandez, J.A., Rangel, A., Hufford, M.B., Gepts, P., Aray-Arroyo, A., Riverabustamante, R., Alvarez-Buylla, E.R., 2009. Transgenes in Mexican maize: molecular evidence and methodological considerations for GMO detection in landrace populations. Mol. Ecol. 18, 750-761. http://doi:10.1111/j.1365-294X.2008.03993.x.

Powell, J.R., Levy-Booth, D.J., Gulden, R.H., Asbil, W.L., Campbell, R.J., Dunfield, K.E., Hamill, A.S., Hart, M.M., Lerat, S., Nurse, R.E., Pauls, K.P., Sikkema, P.H., Swanton, C.J., Trevors, J.T., Klironomos, J.N., 2009. Effects of genetically modified, herbicide-tolerant crops and their management on soil food web properties and crop litter decomposition. J. Appl. Ecol. 388-396. http://doi:10.1111/j.1365-2664.2009.01617.x.

Pusztai, A., Koninkx, J., Hendriks, H., Kok, W., Hulscher, S., Van Damme, E.J.M., Peumans, W.J., Grant, G., Bardocz, S., 1996. Effect of the insecticidal *Galanthus nivalis* agglutinin on metabolism and the activities of brush border enzymes in the rat small intestine. J. Nutritional Biochem. 7, 677. doi:10.1016/S0955-2863(96)00131-3.

Qi, X., Chen, S., Sheng, Y., Guo, M., Liu, Y., He, X., Huang, K., Xu, W., 2015. Safety assessment of genetically modified rice expressing human serum albumin from urine metabonomics and fecal bacterial profile. Food Chem. Toxicol. 76, 1-10.

Qi, X., He, X., Luo, Y., Li, S., Zou, S., Cao, S., Tang, M., Delaney, B., Xu, W., Huang, K., 2012. Subchronic feeding study of stacked trait genetically-modified soybean (3Ø5423 × 40-3-2) in Sprague-Dawley rats. Food Chem. Toxicol. 50, 3256-3263.

Raybould, A., Higgins, L.S., Horak, M.J., Layton, R.J., Storer, N.P.,Fuente, J.M.D., Herman, R,A., 2012. Assessing the ecological risks from the persistence and spread of feral populations of insect-resistant transgenic maize. Transgenic Res. 21, 655-664. doi: 10.1007/s11248-011-9560-4.

Reiting, R., Grohmann, L., Moris, G., Made, D., 2013. Detection and characterization of an unknown rice event in Basmati rice products. Eur. Food Res. Technol. 236, 715-723.

Sanchez, M.A., Cid, P., Navarrete, H., Aguirre, C., Chacon, G., Salazar, E., Prieto, H., 2016. Outcrossing potential between 11 important genetically modified crops and the Chilean vascular flora. J. Plant Biotech. 14, 625-637.

Schulze, J., Frauenknecht, T., Brodmann, P., Bagutti, C., 2014. Unexpected Diversity of Feral Genetically Modified Oilseed Rape (*Brassica napus* L.) Despite a Cultivation and Import Ban in Switzerland. PLoS One. 9, e114477. doi: 10.1371/journal.pone.0114477.

Sears, M.K., Hellmich, R.L., Stanley-Horn, D.E., Oberhauser, K.S., Pleasants J.M., Mattila, H.R., Siegfried, B.D., Dively, G.P., 2001. Impact of *Bt* corn pollen on monarch butterfly populations: A risk assessment. Proc. Natl. Acad. Sci. U.S.A. 98, 11937-11942. 10.1073/pnas.211329998.

Seralini, G.E., Clair, E., Mesnage, R., Gress, S., Defarge, N., Malatesta, M., Hennequin, D., de Vendômois, J.S., 2012. Long term toxicity of a Roundup herbicide and a Rounduptolerant genetically modified maize. Food Chem. Toxicol. 50, 4221-4231. Retraction in: Food Chem. Toxicol. 2014; 63:244.

Seralini, G.E., Mesnage, R., Defarge, N., Gress, S., Hennequin, D., Clair, E., Malatesta, M., de Vendômois, J.S., 2013. Answers to critics: Why there is a long term toxicity due to a Roundup-tolerant genetically modified maize and to a Roundup herbicide. Food Chem. Toxicol. 53, 476-483. Env. Sci. Europe. 26.

Seralini, G.E., Clair, E., Mesnage, R., Gress, S., Defarge, N., Maltesta, M., Hennequin, D., De Vendomois, J.S., 2014. Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerantgenetically modified maize. DOI: 10.1186/s12302-014-0014-5.

Serrat, X., Esteban, R., Penas, G., Catala, M.M., Mele, E., Messeguer, J., 2013. Direct and reverse pollen-mediated gene flow between GM rice and red rice weed. AoB PLANTS 5: plt050; doi:10.1093/aobpla/plt050.

Sheng, Y., Qi, X., Liu, Y., Guo, M., Chen, S., He, X., Huang, K., Xu, W., 2014. Subchronic toxicity study in vivo and allergenicity study in vitro for genetically modified rice that expresses pharmaceutical protein (human serum albumin). Food Chem. Toxicol. 72, 242-246.

Singhal, K.K., Tyagi, A.K., Rajput, Y.S., et al. 2011. Feed intake, milk production and composition of crossbred cows fed with insectprotected Bollgard II cottonseed containing Cry1Ac and Cry2Ab proteins. Animal. 5, 1769-73.

Song, H., He, X., Zou, S., Zhang, T., Luo, Y., Huang, K., Zhu, Z., Xu, W., 2015. A 90-day subchronic feeding study of genetically modified rice expressing Cry1Ab protein in Sprague-Dawley rats. Transgenic Res. 24, 295-308.

Song, Y., Liang, C., Wang, W., Fang, J., Sun, N., Jia, X., Li, N., 2014. Immunotoxicological evaluation of corn genetically modified with *Bacillus thuringiensis* Cry1Ah gene by a 30-day feeding study in BALB/c mice. PLoS One.9, e78566.

Southgate, E.M., Davey, M.R., Power, J.B., Merchant, R., 1995. Factors affecting the genetic engineering of plants by microprojectile bombardment. Biotechnol. Adv. 13, 631-657.

Stagg, N.J., Thomas, J., Herman, R.A., Juberg, D.R., 2012. 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. Regul. Toxicol. Pharmacol. 62, 363-370.

Suzie, K., Ma, J.K.C., Drake, P.M.W., 2008. Genetically modified plants and human health. J. R. Soc. Med. 101, 290-298. DOI 10.1258/jrsm.2008.070372

Szenasi, A., Palinkas, Z., Zalai, M., Schmitz, O.J., Balog, A., 2014. Short-term effects of different genetically modified maize varieties on arthropod food web properties: an experimental field assessment. Scientific Reports. 4, 5315. http://doi:10.1038/srep05315.

Tabashnik, B.E., 2015. ABCs of Insect Resistance to *Bt*. PLoS Genet. 11, e1005646. doi:10.1371/journal.pgen.1005646.

Taheri, F., Azadi, H., DHaese, M., 2017. A world without hunger: organic or GM crops? Sustainability. 9, 580. doi:10.3390/su9040580.

Tang, X., Han, F., Zhao, K., Xu, Y., Wu, X., Wang, J., Jiang, L., Shi, W., 2012. A 90-day dietary toxicity study of genetically modified rice T1C-1 expressing Cry1C protein in Sprague Dawley rats. PLoS One. 7, e52507.

Tappeser, B., Reichenbecher, W., Teichmann, H., 2014. Agronomic and environmental aspects of the cultivation of genetically modified herbicide-resistant plants. A BfN-FOEN-EAA-Joint paper.

Tsatsakis, A.M., Nawaz, M.A., Kouretas, D., Balias, G., Savolainen, K., Tutelyan, V.A., Golokhvast, K.S., Lee, J.D., Yang, S.H., Chung, G., 2017a. Environmental impacts of genetically modified plants: A review. Food Chem. Toxicol. In press. http://dx.doi.org/10.1016/j.envres.2017.03.011.

Tsatsakis, A.M., Docea, A.O., Tsitsimpikou, C. 2016. New challenges in risk assessment of chemicals when simulating real exposure scenarios; simultaneous multi-chemicals' low dose exposure. Food Chem. Toxicol. 96, 174-176.

Tsatsakis, A.M., Lash, L.H., 2017b. Toxicology: the basic science for human well-being and environmental health. Toxicol. Rep. In press; http://dx.doi.org/10.1016/j.toxrep.2017.01.002

Docea, A.O., Calina, D., Goumenou, M., Neagu, M., Gofita, E., Tsatsakis A. 2016. Study design for the determination of toxicity from long-term-low-dose exposure to complex mixtures of pesticides, food additives and lifestyle products Toxicol. Lett. 258, (Suppl 16):S179.

Tsatsakis, A.M., Kouretas, D., Tzatzarakis, M.N., Stivaktakis, P., Tsarouhas, K., Golokhvast, K.S., Rakitskii, V.N., Tutelyan, V.A., Hernandez, A.F., Rezaee, R., Chung, G., Fenga, C., Engin, A.B., Neagu, M., Arsene, A.L., Docea, A.O., Gofita, E., Calina, D., Taitzoglou, I., Liesivuori, J., Hayes, A.W., Gutnikov, S., Tsitsimpiko, C. 2017c. Simulating real life exposures to uncover possible risks to human health: A proposed consensus for a novel methodological approach. Hum. Exp. Toxicol. In press; DOI: 10.1177/0960327116681652.

Tyshko, N.V., Zhminchenko, V.M., Selyaskin, K.E., Pashorina, V.A., Utembaeva, N.T. and Tutelyan, V.A. (2014) Assessment of the Impact of Genetically Modified LibertyLink® Maize on Reproductive Function and Progeny Development of Wistar Rats in Three Generations. *Toxicology Reports*, **1**, 330-340. http://dx.doi.org/10.1016/j.toxrep.2014.05.013

Tyshko, N.V., Sadykova, E.O. Regulation of Genetically Modified Food Use in the Russian Federation//Regulation of Genetically Modified Food Use in the Russian Federation. Food and Nutrition Sciences. – 2016. – V. 7. – P. 743-751. http://dx.doi.org/10.4236/fns.2016.79075

US-EPA (U.S. Environmental Protection Agency).2016. Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. Office of Pesticide Programs. Washington, DC.Vinicius, P., Venancio, Joao Paulo, L., Silva, Alaor A., Almeida, Maisa, R. P. L., Brigagao & Luciana Azevedo., 2012. Conventional (MG-BR46 Conquista) and Transgenic (BRS Valiosa RR) Soybeans Have No Mutagenic Effects and May Protect Against Induced-DNA Damage in Vivo. Nutrition and Cancer. 64, 725-731.

Waigmann, E., Paoletti, C., Davies, H., Perry, J., Kärenlampi, S., Kuiper, H., 2012. Risk assessment of Genetically Modified Organisms (GMOs). EFSA Journal. 10, s1008. DOI: 10.2903/j.efsa.2012.s1008

Walsh, M.C., Buzoianu, S.G., Gardiner, G.E., et al. 2012. Effects of short-term feeding of *Bt* MON810 maize on growth performance, organ morphology and function in pigs. Br. J. Nutr. 107, 364-71.

Wang, E.H., Yu, Z., Jia, X.D., Zhang, W.Z., Xu, H.B., 2016. Effects of parental dietary exposure to GM rice TT51 on the male reproductive system of rat offspring. Biomed. Environ. Sci. 29, 267-274. DOI: 10.3967/bes2016.034.

Wang, E.H., Yu, Z., Hu, J., Xu, H.B., 2013. Effects of 90-day feeding of transgenic *Bt* rice TT51 on the reproductive system in male rats. Food Chem. Toxicol. 62, 390-396.

Wang, X., He, X., Zou, S., Xu, W., Jia, X., Zhao, B., Zhao, C., Huang, K., Liang, Z., 2016. A subchronic feeding study of dicamba-tolerant soybean with the dmo gene in Sprague-Dawley rats. Regul. Toxicol. Pharmacol. 77, 134-142.

Warwick, S.I., Legere, A., Simard, M.J., James, T., 2008. Do escaped transgenes persist in nature? The case of an herbicide resistance transgene in a weedy Brassica rapa population. Mol Ecol. 17, 1387-95.

Watrud, L.S., Lee, E.H., Fairbrother, A., Burdick, C., Reichman, J.R., Bollman, M., Storm, M., King, G., Van de Water, P.K., 2004. Evidence for landscape-level, pollen-mediated gene flow from genetically modified creeping bentgrass with CP4 EPSPS as a marker. Proc. Natl. Acad. Sci. USA. 101, 14533-8.

Wrinn, K.M., Evans, S.C., Rypstra, A.L., 2012. Predator cues and an herbicide affect activity and emigration in an agrobiont wolf spider. Chemosphere. 87, 390-3966. doi:10.1016/j.chemosphere.2011.12.030.

Yan, S., Zhu, J., Zhu, W., Li, Z., Shelton, A.M., Luo, J., Cui, J., Zhang, Q., Liu, X., 2015. Pollen-mediated gene flow from transgenic cotton under greenhouse conditions is dependent on different pollinators. Sci. Reports. 5, 15917. http://doi: 10.1038/srep15917.

Yaqoob, A., Shahid, A.A., Samiullah, T.R., Rao, A.Q., Khan, M.A.U., Tahir, S, Mirza, S.A., Husnain, T., 2016. Risk assessment of *Bt* crops on the non-target plant-associated insects and soil organisms. J. Sci. of Food & Agri. 96, 2613-9. doi: 10.1002/jsfa.7661.

Yuan, Y., Xu, W., He, X., Liu, H., Cao, S., Qi, X., Huang, K., Luo, Y., 2013. Effects of genetically modified T2A-1 rice on the GI health of rats after 90-day supplement. Sci. Rep. 3:1962.

Zeljenková, D., Ambrušová, K., Bartušová, M., Kebis, A., Kovrižnych, J., Krivošíková, Z., Kuricová, M., Líšková, A., Rollerová, E., Spustová, V., Szabová, E., Tulinská, J., Wimmerová, S., Levkut, M., Révajová, V., Ševčíková, Z., Schmidt, K., Schmidtke, J., La Paz, J.L., Corujo, M., Pla, M., Kleter, G.A., Kok, E.J., Sharbati, J., Hanisch, C., Einspanier, R., Adel-Patient, K., Wal, J.M., Spök, A., Pöting, A., Kohl, C., Wilhelm, R., Schiemann, J., Steinberg, P., 2014. Ninety day oral toxicity studies on two genetically modified maize MON810 varieties in Wistar Han RCC rats (EU 7th Framework Programme project GRACE). Arch. Toxicol. 88, 2289-2314.

Zeljenkova, D., Alcova, R., Ondrejkova, J., et al., 2016. One-year oral toxicity study on a genetically modified maize MON810 variety in Wistar Han RCC rats (EU 7th Framework programme project GRACE). Archiv. Toxicol. 10, 2531-2562. DOI: 10.1007/s00204-016-1798-4.

Zhang, M., Zhuo, Q., Tian, Y., Piao, J., Yang, X., 2014. Long-term toxicity study on transgenic rice with Cry1Ac and sck genes. Food Chem. Toxicol.63, 76-83.

Zhao, K., Ren, F., Han, F., Liu, Q., Wu, G., Xu, Y., Zhang, J., Wu, X., Wang, Li, P., Shi, W., Zhu, H., Lv, J., Zhao, X., Tang, X., 2016. Edible safety assessment of genetically modified rice T1C-1 for Sprague Dawley rats through horizontal gene transfer, allergenicity and intestinal microbiota. PLOS ONE. 11, e0163352. doi:10.1371/journal.pone.0163352.

Zhou, X.H., Dong, Y., Wang, Y., Xiao, X., Xu, Y., Xu, B., Li, X., Wei, X.S., Liu, Q.Q., 2012. A three generation study with high-lysine transgenic rice in Sprague-Dawley rats. Food Chem. Toxicol. 50, 1902-1910.

Zhou, X.H., Dong, Y., Xiao, X., Wang, Y., Xu, Y., Xu, B., Shi, W.D., Zhang, Y,, Zhu, L.J., Liu, Q.Q., 2011. A 90-day toxicology study of high-amylose transgenic rice grain in Sprague-Dawley rats. Food Chem. Toxicol. 49, 3112-3118.

Zhou, X.H., Dong, Y., Zhao, Y.S., Xiao, X., Wang, Y., He, Y.Q., Liu, Q.Q., 2014. A three generation reproduction study with Sprague-Dawley rats consuming high-amylose transgenic rice. Food Chem. Toxicol. 74, 20-27.

Zhu, H.J., Chen, Y., Li, Y.H., Wang, J.M., Ding, J.T., Chen, X.P., Peng, Y.F., 2015. A 90 day safety assessment of genetically modified rice expressing Cry1Ab/1Ac protein using an aquatic animal model. J. Agric. Food Chem.63, 3627-3633.

Zhu, Y., He, X., Luo, Y., Zou, S., Zhou, X., Huang, K., Xu, W., 2013. A 90-day feeding study of glyphosate-tolerant maize with the G2-aroA gene in Sprague-Dawley rats. Food Chem. Toxicol. 51, 280-287.

Zou, S., Huang, K., Xu, W., Luo, Y., He, X., 2016. Safety assessment of lepidopteran insect protected transgenic rice with cry2A* gene. Transgenic Res. 25, 163-172.

Web References

Hazardous Substances and New Organisms Act 1996, s 40(2)(a)(v) & 40(2)(b)(v). [Last accessed on April 09, 2017]

http://apps.fas.usda.gov/gainfiles/200106/110681034.pdf. [last accessed on April 09, 2017]

http://english.agri.gov.cn/hottopics/bt/201301/t20130115_9551.htm. [Last accessed on February 27, 2017]

http://envfor.nic.in/division/introduction-8. [Last accessed on February 27, 2016]

http://epa.govt.nz/new-organisms/popular-no-topics/Pages/GM-field-tests-in-NZ.aspx. [Last accessed on April 09, 2017] http://igmoris.nic.in/files%5CCoverpage1.pdf. [Last accessed on April 09, 2017]

http://karantina.deptan.go.id/. [Last accessed on April 09, 2017]

http://law.coa.gov.tw/glrsnewsout/EngLawContent.aspx?id=127. [Last accessed on April 09, 2017]

http://law.coa.gov.tw/GLRSnewsout/EngLawContent.aspx?Type=E&id=34. [Last accessed on April 12, 2017]

http://law.coa.gov.tw/GLRSnewsout/EngLawQuery.aspx. [Last accessed on April 09, 2017]

http://law.moj.gov.tw. [Last accessed on April 09, 2017]

http://link.springer.com/article/10.1007/s00003-014-0898-4. [Last accessed on January 01, 2017]

http://npl.ly.gov.tw/do/www/FileViewer?id=6387. [Last accessed on February 27, 2017]

http://onlinelibrary.wiley.com/doi/10.1111/pbi.12155/pdf. [Last accessed on April 09, 2017]

http://supportprecisionagriculture.org/. [Last accessed on February21, 2017]

http://www. Bch.biodic.go.jp/english/cartagena/images/e_cartagena.pdf. [Last accessed on April 09, 2017]

http://www.aatf-africa.org/userfiles/Status-Regulations-GM-Crops_Africa.pdf. [Last accessed on April 09, 2017]

http://www.biosecurity.govt.nz/biosec/pol/bio-act. [Last accessed on April 09, 2017]

http://www.bsn.go.id/. [Last accessed on April 09, 2017]

http://www.comesa.int/. [Last accessed on April 09, 2017]

http://www.daff.gov.za/doaDev/sideMenu/acts/15%20 GMOs%20No15%20% 281997%29.pdf. [Last accessed on April 09, 2017]

http://www.dbtindia.nic.in/. [Last accessed on March 14, 2017]

http://www.deptan.go.id/. [Last accessed on April 09, 2017] http://www.diputados.gob.mx/LeyesBiblio/pdf/LBOGM.pdf. [Last accessed on April 09, 2017]

http://www.ec.gc.ca/. [Last accessed on May 05, 2017]

http://www.fsc.go.jp/english/standardsforriskassessment/gm_kijun_english.pdf. [Last accessed on February 02, 2017]

http://www.fssai.gov.in/Portals/0/Pdf/fssa_interim_regulation_on_Operatonalising_GM_Food_regulation_in_India.pdf. [Last accessed on April 09, 2017]

http://www.gbgindonesia.com/en/main/useful_resources/documents/publications/Indonesia%20Food%20and%20Agricultural%20Import%20Regulations%20and%20Standards%20%202009.pdf. [Last accessed on April 09, 2017]

http://www.japaneselawtranslation.go.jp/law/detail_main?re= 02&vm=02&id=132. [Last accessed on April 09, 2017]

http://www.gob.mx/sagarpa. [Last accessed on April 09, 2017]

http://www.gob.mx/semarnat. [Last accessed on April 09, 2017]

http://www.gov.cn/flfg/2006-03/02/content_215830.htm. [Last accessed on April 09, 2017]

http://www.hc-sc.gc.ca/fn-an/gmf-agm/guidelines-lignesdirectrices/index-eng.php. [Last accessed on April 09, 2017]

http://www.hc-sc.gc.ca/index-eng.php. [Last accessed on April 09, 2017]

http://www.inspection.gc.ca/eng/1297964599443/1297965645317. [Last accessed on April 09, 2017]

http://www.lawphil.net/statutes/repacts/ra2010/ra_10068_2010.html. [Last accessed on April 09, 2017]

http://www.legislation.govt.nz/act/public/1993/0095/latest/DLM314623.html. [Last accessed on April 09, 2017] http://www.legislation.govt.nz/act/public/1997/ 0087/latest/DLM414577.html. [Last accessed on February 17, 2017]

http://www.legislation.govt.nz/act/public/1999/0142/latest/DLM49664.html. [Last accessed on January 01, 2017]

http://www.legislation.govt.nz/act/public/1997/ 0087/latest/DLM414577.html. [Last accessed on April 09, 2017]

http://www.nap.edu/23395. [Last accessed on January 01, 2017]

http://www.ncbp.dost.gov.ph/21-joint-department-circular/32-jdc-final. [Last accessed on February 15, 2017]

http://www.nepad.org/. [Last accessed on January 01, 2017]

http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/legislation-2. [Last accessed on January 01, 2017]

http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/regfactsheets/$FILE/regris.pdf. [Last accessed on January 01, 2017]

http://www.planalto.gov.br/ccivil_03/_Ato2004-2006/2005/Lei/ L11105.htm#art42. [Last accessed on January 01, 2017]

http://www.pom.go.id/. [Last accessed on January 01, 2017]

http://www.tandfonline.com/doi/full/10.4161/gmcr.18905. [Last accessed on January 01, 2017]

http://www.unep.org/biosafety/files/IDNBFrep.pdf. [Last accessed on April 09, 2017]

http://www.unep.org/biosafety/files/KRNBFrep.pdf. [Last accessed on April 09, 2017]

http://www2.fcfar.unesp.br/Home/CIBio/MarcoLegalBras.pdf. [Last accessed on April 09, 2017]

https://www.agric.wa.gov.au/regulation-genetically-modified-crops-australia. [Last accessed on January 01, 2017] https://www.agric.wa.gov.au/regulation-genetically-modified-crops-australia. [Last accessed on April 09, 2017]

https://www.legislation.gov.au/Details/C2011C00539. [Last accessed on April 09, 2017]

https://www.legislation.gov.au/Details/F2011C00732. [Last accessed on April 09, 2017]

https://www.loc.gov. [Last accessed on April 09, 2017]

https://www.loc.gov/law/help/restrictions-on-gmos/restrictions-on-gmos.pdf. [Last accessed on April 09, 2017]

International Survey of Herbicide Resistant Weeds. http://www.weedscience.org. [Last accessed on April 09, 2017]

www.efsa.europa.eu. [Last accessed on February 15, 2017]

www.epa.ie. [Last accessed on April 09, 2017]

www.fda.gov. [Last accessed on February 15, 2017]

http://www.who.int/foodsafety/areas_work/food-technology/faq-genetically-modified-food/en/. [Last accessed on April 09, 2017]

Figure legends

Figure 1. Factors affecting the frequency of gene flow

Figure 2. Area of eight leading countries occupied by GM crops during 2011-2015

Table 1. Recent research on health hazards of GM food and feed

Crop	Trait(s)/gene(s)/event	Target organism	Duration	Testing range	Reference
Rice	High amylose and resistant starch	SD rats	90 days	Hematology, serum chemistry, urinalysis, serum sex hormone level, gross and anatomical pathology	Zhou et al. (2011)
Rice	Bt T2A-1	SD rats	90 days	Urinalysis	Cao et al. (2011)
Maize	Maize 59122	Dairy cows	28 days	Milk production, milk components, body characteristics	Brouk et al. (2011)
Cotton	Bollgard 11	Dairy cows	28 days	Milk production, milk components	Singhal et al. (2011)
Soybean	HT DAS-68416-4	Broiler chickens	42 days	Body weight, feed intake, percent of chilled carcass weight	Herman et al. (2011a)
Maize	DAS-40278–9	Broiler chickens	42 days	Body weight, feed intake, percent of chilled carcass weight	Herman et al. (2011b)
Maize + soybean	DP-O9814O-6 and DP-356O43–5	Broiler Chickens	42 days	Body weight, feed intake, percent of chilled carcass weight	McNaughton et al. (2011a)
Maize + soybean	DP-O9814O-6 and DP-356O43–5	Laying Hens	42 days	Feed intake, egg production, egg component weights	McNaughton et al. (2011b)
Rice	High lysine	SD rats	3 generations	Hematology, serum chemistry, serum sex hormone level, gross and anatomical pathology	Zhou et al. (2012)
Rice	Cry1C	SD rats	90 days	Hematology, blood biochemistry, bacterial count, histopathology	Tang et al. (2012)
Soybean	HT *desaturase-2*, CP4 EPSPS	SD rats	90 days	Hematology, serum chemistry, anatomic pathology	Qi et al. (2012_
Soybean	HT acetohydroxyacid synthase	Wistar rats	91 days	Hematology, serum chemistry, histopathology	Chukwudebe et al. (2012)
Soybean	HT	Swiss mice	15 days	Mutagenicity, oxidative damage	Venancio et al. (2012)
Maize	Bt-38 (Cry1Ac-M)	SD rats	90 days	Body weight, hematology, serum chemistry, anatomic pathology	Liu et al. (2012)
Maize	DAS-40278-9 AAD-1	Mice	28 days	Anatomic pathology, histopathology, hematology	Stagg et al. (2012)
Wheat	GmDREB1	BALB/c mice	30 days	Hematology, serum chemistry	Liang et al. (2012)
Maize	Multivitamin corn	Mice	28 days	Body weight, feed intake, hematology, serum chemistry, histopathology	Arjo et al. (2012)
Maize	MON810	Pig	30 days	Hematology, immune cell phenotyping, antibody response	Walsh et al. (2012)
Rice	Bt rice TT51	Wistar rats	90 days	Hematology, serum chemistry, histopathology	Wang et al. (2013)
Rice	T2A1	SD rats	90 days	Histopathology, hematology, blood chemistry, horizontal gene transfer detection	Yuan et al. (2013)
Maize	DP-004114-3	SD rats	90 days	Clinical anatomic pathology	Delaney et al. (2013)

Maize	DP-004114-3	SD rats	90 days	Clinical anatomic pathology	Hardisty et al. (2013)
Maize	G2-aroA	SD rats	90 days	Body weight, food utilization, serum chemistry, hematology, histopathology	Zhu et al. (2013)
Wheat	TaDREB4	BALB/c mice	30 days	Body weight, hematology, serum chemistry, delayed-type hypersensitivity, mice-carbon clearance test	Liang et al. (2013)
Rice	High amylose and resistant starch	SD rats	3 generations	Body weight, food utilization, serum chemistry, hematology, histopathology	Zhou et al. (2014)
Maize	NK603	SD rats	90 days	Anatomopathological tests, blood chemistry, urinalysis, Tumor incidence, mortality	Seralini et al. (2014)
Rice	Bt rice TT51	Wistar rats	2 generations	Hematology, serum chemistry, histopathology	Wang et al. (2014)
Rice	Cry1Ac + sck	SD rats	546 days	Body weight, food consumption, serum chemistry, pathology	Zhang et al. (2014)
Rice	Human serum albumin	SD rats	90 days	Clinical observation, feed efficiency, hematology, serum chemistry, organ weight	Sheng et al. (2014)
Maize	MON810	Wistar rats	90 days	Physical examination, hematology, clinical biochemistry analyses, gross necropsy and histopathology	Zeljenkova et al. (2014)
Maize	Bt Cry1Ah	Mice	30 days		Song et al. (2014)
Canola	DP-073496-4	SD rats	90 days	Ophthalmology, neurobehavioral assessments, hematology, coagulation, clinical chemistry, urinalysis, gross pathology	Delaney et al. (2014)
Rice	Bt Cry1Ab	SD rats	90 days	Body weight, food intake, hematology and clinical chemistry, pathology, humoral immunity, cellular immunity, non-specific immunity	Song et al. (2015)
Rice	Human serum albumin	SD rats	90 days	Urinalysis, spectroscopy, short chain fatty acid assay, enzyme activity in feces, analysis of bacterial profile	Qi et al. (2015)
Rice	Cry1Ab/1Ac	Broiler chicken	42 days	Chicken growth, serum biochemistry, transgene detection through pcr	Li et al. (2015)
Rice	Cry1Ca	Frog	90 days	Tadpole development, survival, body weight, histopathology	Chen et al. (2015)
Rice	Cry1Ab/1Ac	Frog	90 days	Gross necropsy and histopathology, live and kidney function, Cry1Ab/1Ac content in different body parts	Zhu et al. (2015)
Maize	BT799	SD rats	90 days	Body weight gain and food utilization, hematology, serum chemistry, serum sex hormone levels, sperm mobility and count, sperm morphology, organ weight and histopathology	Guo et al. (2015)
Soybean	Cv127	SD rats and poultry	90 days	Clinical pathology, gross necropsy and histopathology	He et al. (2016)
Maize	Gh5112e-11c	SD rats	90 days	Clinical observations, body weight gain, feed utilization, hematology, serum chemistry, necropsy and histopathology,	Han et al. (2016)
Rice	Cry2A	SD rats	90 days	Body weight, food consumption, hematology, serum chemistry	Zou et al. (2016)
Soybean	MON87708	SD rats	90 days	Body weight, food consumption, clinical observations, hematology, serum chemistry, anatomical pathology	Wang et al. (2016)

Maize	Cry1Ac	Pigs	196 days	Hematology, serum chemistry,	Chen et al. (2016)
Maize	Bt MON810	Albino rats	90 days	Light microscopy, electron microscopy, immunohistochemical study, morphometerical characteristics of jejunal mucosa	Ibrahim et al. (2016)
Maize	MON 87411	CD-1 mice	28 days	Clinical observations, mortality, moribundity, body weight, serum chemistry, hematology, gross examination and necropsy	Petrik et al. (2016)
Rice	TT51	SD rats	70 days	Reproductive system, sperm parameters, testicular function enzyme activities, serum hormones, testis histopathological examination, expression level of genes	Wang et al. (2016)
Rice	T1C-1	SD rats	90 days	Horizontal gene transfer, allergenicity, intestinal microbiota	Zhao et al. (2016)
Rice	CrylAb/lAc	Monkey	1 year	Hematology, blood chemistry, gross necropsy and histopathology, serum metabolome, gut microbiome,	Mao et al. (2016)
Maize	MON810	SD rats	1 year	Physical examination, hematology, clinical biochemistry analyses, gross necropsy and histopathology	Zeljenkova et al. (2016)
Maize	y-TMT	SD rats	90 days	Body weight, food consumption, hematology, serum chemistry, histopathology,	Fang et al. (2017)
Maize	DKC 2678 Roundup-tolerant NK603	SD rats	2 Years	Transcriptome analysis, Metabolome analysis	Mesnage et al. (2017)
Rice	Cry1Ac and sck	SD rats	Two generations	Gross necropsy, organ weights, histopathology, serum biochemistry	Hu et al. (2017)

SD = Sprague Dawley

Table 2. Summary of global regulatory authorities, primary legislation and available regulatory guidance

Country (Region)	**Regulatory Authority(s)**	***Primary legislation***	**Accessible link(s)**	**Regulatory Guidance (if available)**	
South Africa	Common Market for Eastern and Southern Africa National Biosafety Network of Expertise (ABNE)	*GMO Act 1997*	http://www.comesa.int/ http://www.nepad.org/	http://www.daff.gov.za/doaDev/sideMenu/acts/15%20GMOs%20No15%20%281997%29.pdf. http://www.aatf-africa.org/userfiles/Status-Regulations-GM-Crops_Africa.pdf	https://www.loc.gov/law/help/restrictions-on-gmos/restrictions-on-gmos.pdf https://www.loc.gov
Brazil	National Technical Commission (CTNBio) Internal Biosafety Committees (CIBio) National Biosafety Council (CNBS) Ministry of Agriculture and Livestock (MAPA) National Agency for Sanitary Surveillance (ANVISA) Brazilian Institute of Environment and Renewable Natural Resources (IBAMA)	*Law No. 11,105 of March 24, 2005* *Law No. 8,078 of September 11, 1990* *Decree No. 4,680 of April 24, 2003*	http://www.planalto.gov.br/ccivil_03/_Ato2004-2006/2005/Lei/L11105.htm#art42.	http://www2.fcfar.unesp.br/Home/CIBio/MarcoLegalBras.pdf	
China	Ministry of Agriculture (MOA) GMO Biosafety Committee	*Regulations on Administration of Agricultural Genetically Modified Organisms Safety*	http://english.agri.gov.cn/hottopics/bt/201301/t20130115_9551.htm	http://apps.fas.usda.gov/gainfiles/200106/110681034.pdf http://www.gov.cn/flfg/2006-03/02/content_215830.htm	

Australia New and Zealand	Office of the Gene Technology Regulator (OGTR) Environmental Protection Authority (EPA) Food Standards Australia New Zealand (FSANZ)	*Gene Technology Act 2000* *The Australia New Zealand Food Safety Code* *Resource Management Act 1991* *Hazardous Substances and New Organisms Act 1996* *The Biosecurity Act 1993* *The Australia New Zealand Food Safety Code* *The Animal Welfare Act 1999* *The Agricultural Compounds and Veterinary Medicines Act 1997*	https://www.legislation.gov.au/Details/C2011C00539 https://www.legislation.gov.au/Details/F2011C00732 http://www.legislation.govt.nz/act/public/1999/0142/latest/DLM49664.html. http://www.legislation.govt.nz/act/public/1997/0087/latest/DLM414577.html. http://www.legislation.govt.nz/act/public/1997/0087/latest/DLM414577.html. Hazardous Substances and New Organisms Act 1996, s 40(2)(a)(v) & 40(2)(b)(v). http://www.legislation.govt.nz/act/public/1993/0095/latest/DLM314623.html. http://www.biosecurity.govt.nz/biosec/pol/bio-act	https://www.agric.wa.gov.au/regulation-genetically-modified-crops-australia http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/legislation-2 http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/regfactsheets/$FILE/regris.pdf http://epa.govt.nz/new-organisms/popular-no-topics/Pages/GM-field-tests-in-NZ.aspx https://www.agric.wa.gov.au/regulation-genetically-modified-crops-australia	
United States	1. Environment Protection Agency (EPA) 2. Food and Drug Administration (FDA) 3.United States Department of Agriculture (USDA)	*FIFRA Act* *FFDCA Act* *National Environmental Policy Act*	www.epa.ie www.fda.gov	http://www.nap.edu/23395	
Europe	European Food Safety Authority		www.efsa.europa.eu	http://link.springer.com/article/10.1007/s00003-014-0898-4	
Canada	1. Health Canada	*Foods and Drug*	http://www.hc-sc.gc.ca/index-	http://www.hc-sc.gc.ca/fn-	

	2. Canadian Food Inspection Agency (CFIA) 3. Environment Canada	*act 1985* *Food and Drug regulations* *The regulation of GM food* *The plant protection act 1990* *Plant protection regulations* *Seeds act 1985* *Seed regulations (PartV)*	eng.php http://www.inspection.gc.ca/eng/1297964599443/1297965645317 http://www.ec.gc.ca/	an/gmf-agm/guidelines-lignesdirectrices/index-eng.php	
Mexico	Secretariat De Agricultura, Candaeria, Desarrollo Rural, Pesca Y Alimentacion (SAGARPA) Commission on Biosecurity of GMO	*GMO Law*	http://www.gob.mx/semarnat http://www.gob.mx/sagarpa	http://www.diputados.gob.mx/LeyesBiblio/pdf/LBOGM.pdf	
Argentina	National Advisory Commission on Agricultural Biotechnology (CANABIA) Biotechnology Directorate National Service for Agrifood Helath and Quality (SENASA) Agriculture Market Directorate			http://www.tandfonline.com/doi/full/10.4161/gmcr.18905	
India	Genetic Engineering and Appraisal Committee Ministry of Environment and Forests Ministry of Agriculture Department of	*FSSA Rules, 2009* *EPA Rules, 1989* *Biological Diversity Rules, 2004* *The Seed Policy,*	http://www.dbtindia.nic.in/ http://envfor.nic.in/division/introduction-8	http://igmoris.nic.in/files%5CCoverpage1.pdf http://onlinelibrary.wiley.com/doi/10.1111/pbi.12155/pdf http://www.fssai.gov.in/Portals/0/Pdf/fssa_interim_regulation	

	Biotechnology & Ministry of Science and Technology Indian Council for Agricultural Research Protection of Plant Variety and Farmer's Right Authority	*2002* *The Seeds Rule, 1968* *PPVFRA Rules, 2003*		_on_Operatonalising_GM_Food_regulation_in_India.pdf	
Indonesia	Ministry of Agriculture Agency of Agricultural Quarantine National Agency of Drugs and Food Control National Standardization Agency	*Food Law No. 7/1996* *Agricultural Minister Regulations, 1997* *Joint Minister Decree, 1999* *Government Regulation No. 28/2004, 21/2005* *National Agency of Drug and Food Control Regulation, 2008* *Presidential Regulation No. 39/2010* *Food Law no. 18/2012*	http://www.deptan.go.id/ http://karantina.deptan.go.id/ http://www.pom.go.id/ http://www.bsn.go.id/	http://www.unep.org/biosafety/files/IDNBFrep.pdf http://www.gbgindonesia.com/en/main/useful_resources/documents/publications/Indonesia%20Food%20and%20Agricultural%20Import%20Regulations%20and%20Standards%20-%202009.pdf	
Japan	Ministry of Agriculture, Forestry and Fisheries (MAFF) Ministry of Health, Labor and Welfare (MHLW) Ministry of Education, Culture, Sports, Science and	*Cartagena Act*		http://www.japaneselawtranslation.go.jp/law/detail_main?re=02&vm=02&id=132 http://www. Bch.biodic.go.jp/english/cartagena/images/e_cartagena.pdf. http://www.fsc.go.jp/english/st	

	Technology (MEXT)			andardsforriskassessment/gm_kijun_english.pdf	
Philippines	National Committee on Biosafety of the Philippines (NCBP) Department of Science and Technology Department of Agriculture Department of Environment and Natural Resources Department of Health Department of Interior and Local Government National Biosafety Framework	*Joint Department Circular No.1, series of 2016 (JDC 01-2016)* *Organic Agriculture Act of 2010*	http://www.ncbp.dost.gov.ph/21-joint-department-circular/32-jdc-final	http://www.lawphil.net/statutes/repacts/ra2010/ra_10068_2010.html	
South Korea	Ministry of Science, Information, Communication, Technology & Future Planning (MSIP) Ministry of Health & Welfare (MW) Ministry of Environment (ME) Ministry of Agricultural, Food & Rural Affairs (MAFRA) Ministry of Oceans & Fisheries (MOF) Ministry of Food and Drug Safety (MFDS)	*Cartagena Act* *LMO Act 2001* *Unified Enforcement Regulation*		http://www.unep.org/biosafety/files/KRNBFrep.pdf	
Taiwan	Ministry of Health and Welfare	*Act Governing Food Senitation*	http://npl.ly.gov.tw/do/www/FileViewer?id=6387	http://law.coa.gov.tw/GLRSnewsout/EngLawQuery.aspx	

			http://law.moj.gov.tw	http://law.coa.gov.tw/GLRSnewsout/EngLawContent.aspx?Type=E&id=34 http://law.coa.gov.tw/glrsnewsout/EngLawContent.aspx?id=127	
Russia	Ministry of Agriculture Ministry of Healthcare Federal Service for Surveillance of consumer rights Protection Federal Service for Veterinary and Phytosanitary Surveillance	*No specific Law available*			

Figure 1. Factors affecting the frequency of gene flow

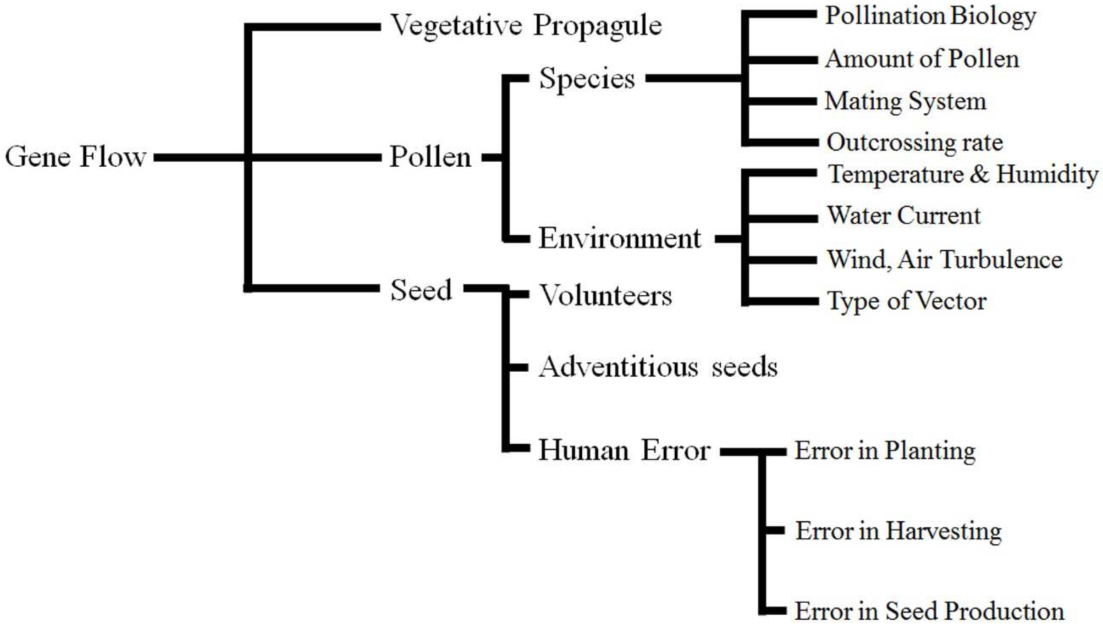
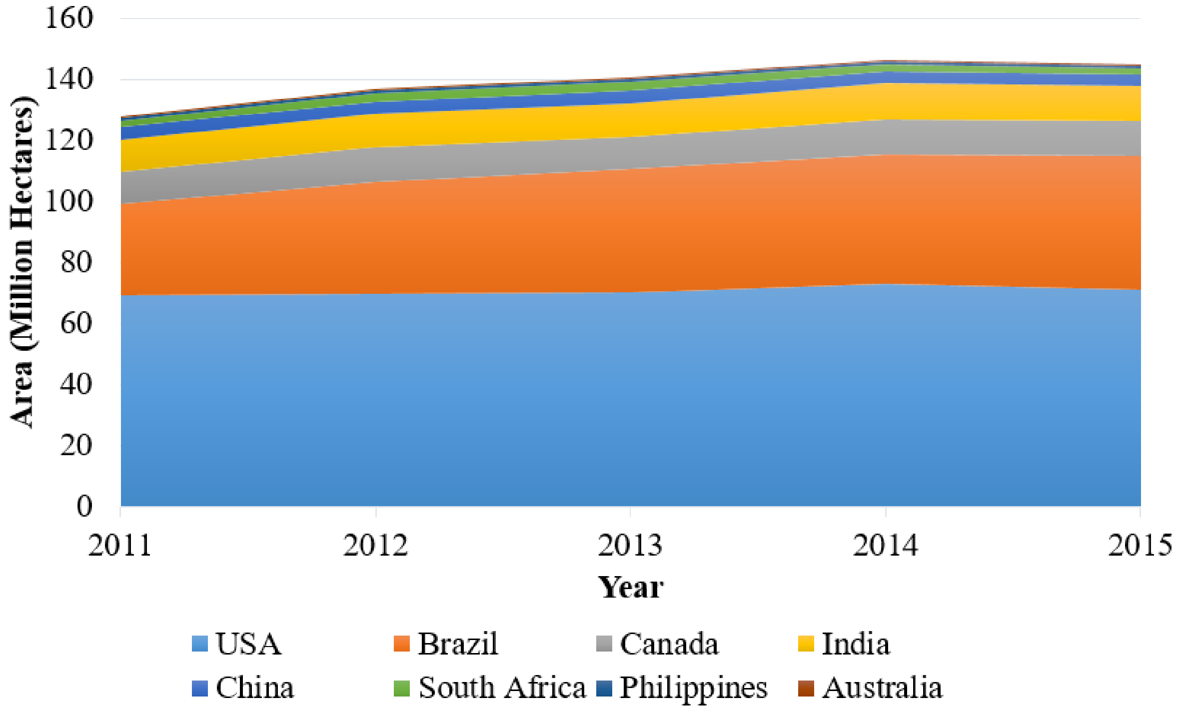


Figure 2. Area of eight leading countries occupied by GM crops during 2011-2015



Highlights

1. Gene flow is a hostile force and there are possible risks of development of genetically modified (GM) plants × wild progenitor hybrids.
2. Biodiversity is affected by cultivation of GM crops, especially herbicide resistant crops.
3. Currently available data related to toxicity of GM food and feed to health is insufficient and controversial.
4. The “consensus” over the GM safety is a falsely perpetuated construct.
5. Current protocols to investigate toxicity of GM food and feed should be improved with respect to exposure time and cumulative toxicity of different GM food/feed mixtures.
6. Global political stance and regulations are presented.