Cropland Policy Mtg
2/9/2016
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The nonsensical GMO pseudo-category and a precautionary rabbit hole

To the Editor:

The term genetically modified organisms (GMOs) is a useless and imprecise category used to pigeonhole products (mostly crops) that have had their genetic content engineered to cancel undesirable phenotypic traits (e.g., allergenicity or toxicity) or to express desired added traits (e.g., resistance to pests, herbicide tolerance, improved nutritional properties or better performance under abiotic stress, such as flooding, drought or heat). It is theoretically and practically impossible to precisely specify a supposed common denominator for all these products; thus, the awkwardness and contradictions of the two main current pseudo-definitions by the European Union[1] (Brussels) and the Cartagena Protocol[2]. On the one hand, these two botched regulations lump together, in a very mixed pile, a whole range of 'green' biotech products with very different characteristics just because they all have spliced DNA; on the other, they omit everything with often similar or identical properties, obtained through genetic manipulation that is neither direct nor targeted (e.g., traditional cross-breeding and hybridizations, cell culture, and physical or chemical mutagenesis).

As formulated in the *Rio Declaration on Environment and Development*, the precautionary principle (PP) states: "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation"[3]. Originally created with the aim of protecting the environment, the PP has subsequently been broadened by the European Union to cover also policies for safeguarding consumers, and human, animal and plant health. However, the PP has sometimes been invoked inappropriately, for example, in situations of generic, undefined alarm. For this reason, the European Commission (Brussels) recommends: "A decision to invoke the PP does not mean that the measures will be adopted on an arbitrary or discriminatory basis"; instead, a decision to apply the PP should be based on "detailed scientific and other objective information"[4]. That is not the case for GMOs. Any attempt to apply the PP to this fake container as a supposed coherent object is meaningless. Nowhere is this more evident than in a recent paper entitled "The precautionary principle (with application to the genetic modification of organisms)," the main author of which is renowned scholar and popular author Nassim Nicholas Taleb[5].

In the very first sentence of the paper, Taleb *et al.*[5] seek to reformulate the meaning of PP. Thus, in the authors' view, the PP "states that if an action or policy has a suspected risk of causing severe harm to the public domain (affecting general health or the environment globally), the action should not be taken in the absence of scientific near-certainty about its safety." This is a major change in the spirit and the letter of the original and extended principle. The PP does not recommend waiting for near-certainty about the safety or health impact of the possible action that implies a suspected risk (which, moreover, can be local, not global); instead, it says that the lack of scientific certainty about the risk of an action must not in itself preclude states from intervening in order to contain such a risk preventatively. Even if the authors' reformulation of the PP definition were acceptable, they do not provide a clear justification for it.

In any case, for argument's sake, let us accept their re-interpretation of the PP—a principle that, the authors state, must be invoked only when extreme danger is predicated, the consequences of which "can involve total irreversible ruin, such as the extinction of human beings or all life on the planet"[5]. Thus, we understand that the PP should, in short, be applied only in the case of an apocalyptic prospect. To distinguish the cases in which the PP should not be applied, and those instead where it must be considered applicable, the article enters into a detailed eight-page discussion on the assessment of risks—which may be more or less catastrophic—of human activities, with particular regard to planetary environmental scenarios. We won't enter into the merits of their explanation; let us accept it *en bloc*, and turn to the applications they choose for discussion.

The authors consider two areas where they argue their definition of the PP might be applied; nuclear energy and GMOs. The parallels drawn between nuclear energy and GMOs are—not to put too fine a point on it—bewildering. If these academics had compared the risk of radioactive pollution with that of pathogenic or weaponized microorganisms, it might have made some sense; instead, we are informed that the risk of nuclear holocaust is "local" and not overly important because it has been thoroughly studied. Thus, the PP is not applicable to nuclear energy.

GMOs, in contrast, are another story. They "have the propensity to spread uncontrollably, and thus their risks cannot be localized." GMOs are a cataclysm waiting to happen and thus should be placed under the PP. Bizarre nonsense. Taleb *et al.*[5] have no appreciation that GMOs are not a thing *per se*—they are simply an ill-labeled group of things (those in agriculture being most commonly in the public eye) produced in certain ways, each of which has a unique profile of risks and benefits. No GMO plant, or any other vegetable for that matter, is capable of spreading uncontrollably across the planet.

The authors go on to rail against newfangled GMO foods that conflict with "human experience over generations," which "has chosen the biological organisms that are relatively safe for consumption." The latter is true apparently because safe biological organisms "were subject to selection over long times and survived." This is often not the case. Plenty of the completely untested non-GMO foods that we eat today were created in the past few decades—even in very recent days—using radiation or chemicals.

As an example of the pervasive threat of GMOs in the food chain, they discuss transgenic maize—a very common crop in the United States, the derivatives of which (e.g., syrup, oil, starch) are widespread; therefore, "the modification of crops impacts everyone"[5]. Let us allow that everyone eats DNA-spliced maize. And so? The derivatives from transgenic maize are exactly the same as those from unmodified maize: syrup, oil, starch. It is in fact impossible to determine whether such derivatives come from transgenic maize or nontransgenic maize. Are the authors seriously proposing then that processed ingredients from approved transgenic maize are potentially catastrophic, whereas the same processed ingredients from traditional maize are not?

The paper is even more disconcerting as it goes on: "The systemic global impacts of GMOs arise from a combination of (i) engineered genetic modifications, (ii) monoculture—the use of single crops over large areas"[5]. No. This combination does not happen often, and where it happens nothing changes. Extensively cultivated single crops can exist without being genetically modified (e.g., oil palms in Indonesia); they can be pre-existing, and only subsequently be DNA-spliced to add a trait (e.g., alfalfa, a grass for fodder, which has been made tolerant to herbicides in the United States; flax, similarly, in Canada). Also every trait is crossed into tens to hundreds of landraces that perform best in a certain environmental and regional context—hardly "monoculture." Do these pre-existing crops perhaps change their nature, becoming ready to "spread uncontrollably," when we add a useful trait through a slight readjustment to their DNA? And in addition, there are numerous small local and typical crops (above all fruit and vegetables), for which genetic engineering solutions are available to protect or improve them in various ways; many are still not applied due to the excessive costs linked to the regulatory nightmare that retards development of GMOs. The claimed link between genetic engineering and extensive monocultivation is not at all necessary, and where there is such a link, it is banal. Consequently, the grounds for the alleged "systemic impact" of GMOs does not exist.

The piece contains other errors of scholarship. Let us look at just the biggest blunder. The authors confuse traits that confer resistance to pests with traits that render crops tolerant to herbicides. They state that the recombination of plant DNA involves "modifying its resistance to other chemicals such as herbicides or pesticides"[5]. Now, "resistance to pesticides," with reference to plants, means nothing; pests, not vegetables, may evolve resistance to pesticides. In fact, a trait that can be included in vegetal organisms is resistance to certain pests (through specific endogenous toxins), which makes the external use of the related pesticides unnecessary. All the authors need is to be just a little better informed, to avoid talking nonsense. Here we can see that these prophets of the doom ("ruin") that will undoubtedly follow from GMOs do not even understand the elementary distinction between the two traits that are most frequently inserted into DNA-spliced crops (resistance to pests and tolerance of herbicides).

They also introduce nonsequiturs, such as Golden Rice not being a panacea for food security; Chinese subjects failing to be fully informed in a GM rice test; agribusiness creating GMOs for profit. All points for debate in themselves, but how do they relate to their catastrophic PP and its applicability to GMOs?

It seems that Taleb *et al.*[5] are intent on leading us down the rabbit hole—the rabbit hole that takes us to fields where DNA-spliced sugar beets propagate endlessly, while their conventionally bred 'cousins' calmly stay put. In this, the authors' alternative, fictional universe, we should be terrified when faced with a field of Amflora (transgenic) potatoes, but feel safe if the same field contains instead Super potatoes (mutagenized), even if the two varieties express the same phenotype—absence of a certain type of starch. We should erect a safety cordon around the field of Roundup Ready or LibertyLink maize (transgenic and tolerant to two distinct herbicides) but frolic in the adjacent field of Clearfield maize (mutagenized to be tolerant to a different type of herbicide). We should gag on the toxic, harmful and poisonous oil from transgenic canola, but lap up the identical and indistinguishable oil squeezed from seeds whose 'ancestors' were mutagenized.

To summarize, the Taleb *et al.*[5] article bolsters ignorance and continues the spread of misinformation. The confused humbug, mixed with errors and basic misunderstandings, appears to be the latest proof of the inexplicable and perverse fascination of the pseudo-category of GMOs, to which even opinion leaders and intellectuals are susceptible.

COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

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Wm. Adams

Statement from William W. Adams III, Professor, Department of Ecology & Evolutionary Biology, University of Colorado, Boulder, CO on **Genetically Engineered Crops**

The scientific evidence has clearly shown the many benefits of genetically engineered crops and plants, with no credible evidence of harm. 1) Increased yields with fewer inputs (the very goal of a more sustainable approach to agriculture), 2) decreased pollution of the environment, 3) decreased use of fossil fuels and therefore 4) decreased emission of greenhouse gasses, increased practice of no-till agriculture [and all of the benefits that brings with it, including better stewardship of agricultural land, e.g., 5) decreased CO_2 emissions from the soil, 6) increased soil water retention, 7) increased soil nutrient retention, and 8) decreased erosion and loss of soil], 9) greater income for farmers, 10) lower prices for consumers (the latter two both derived from the greater yields), 11) the preservation of natural environments that might otherwise have been plowed under to feed the ever-growing human population (had the farmers not seen the increased yields that have resulted from the adoption of the engineered crops), 12) the increased income that organic farmers have seen as a result of the effectiveness of the Bt crops in dramatically decreasing the level of insects that feed on the crops (organic farmers have actually seen a greater economic benefit than the farmers paying the extra cost for the engineered seed! See Hutchison et al. 2010 below), 13) in some cases crops that are safer because of reduced levels of mycotoxins that are poisonous to humans (again as a result of the Bt crops that have so dramatically decreased the insect damage to the crops, which in turn decreases the pathogen damage to crops - mycotoxins accumulate in crops infected with pathogenic fungi, and the pathogens are carried by the insects and infect crops at the sites that are opened when the insects munch on the crops), 14) a cleaner and safer working environment for the farmers that no longer have to handle the really nasty insecticides and herbicides (which is also better for those individuals in close proximity to the fields where they might have encountered clouds of the pesticides in the past), 15) the huge benefit to the farmers in developing countries (more farmers in third world countries plant genetically engineered crops than in the developed countries, with a greater economic return than those in developed countries, and this divide has continued to grow over the past several years), which has also 16) benefited the economies and the consumers of those third world countries.

So many farmers would not have voluntarily chosen to switch to genetically engineered crops if there were not clear benefits. Even the Amish, who want nothing to do with technology, adopted genetically engineered corn a number of years ago because of all of the benefits. The only reason to push for mandatory labels is to vilify those products, demonize the companies that are providing the seeds to the farmers who chose to purchase and grow them, and to instill more fear in the public. This is indeed part of the war on science, as National Geographic pointed out in the cover story to their March 2015 issue (along with the climate change skeptics, fear mongers concerning vaccinations, and evolution deniers, among others). We should base our discussions and decision-making on evidence and rationale thought, not on unfounded concerns and fears or some misplaced distrust of capitalism and large corporations. If the latter is the target, then the laws should be the focus of change (to socialism and away from capitalism) and taxes should be raised so that the engineering of crops can be publicly funded and the products made available to all. Organic farmers should be free to farm organically, and, since it is not illegal to do so, those who wish to farm with genetically engineered crops should be free to do so. It would be unethical to prevent a farmer to exercise her or his right to farm in the most sustainable way possible.

DEBATE – Intelligence^2 Debate on the proposition "Genetically Modify Food". Involving Alison Van Eenennaam (see third reference below). Outcome? The largest shift in opinion (from 32% to 60% in favor) in the history of this program. Also beginning of Bill Nye's shift from opposition to support of genetically engineered crops. See: http://intelligencesquaredus.org/debates/past-debates/item/1161-genetically-modify-food

SAFETY FOR CONSUMPTION

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SUSTAINABILITY – ENVIRONMENTAL, SOCIETAL, AND ECONOMIC BENEFITS through DECREASED USE of PESTICIDES, SWITCHING to LESS TOXIC and MORE RAPIDLY DEGRADED HERBICIDES, INCREASED NO-TILL (CONSERVATION TILLAGE) AGRICULTURE, DECREASED EMISSION of CO_2 and OTHER POLLUTANTS, and INCREASED YIELDS

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Wm. Adams

Presentation to Boulder County Commissioners, 9 February 2016

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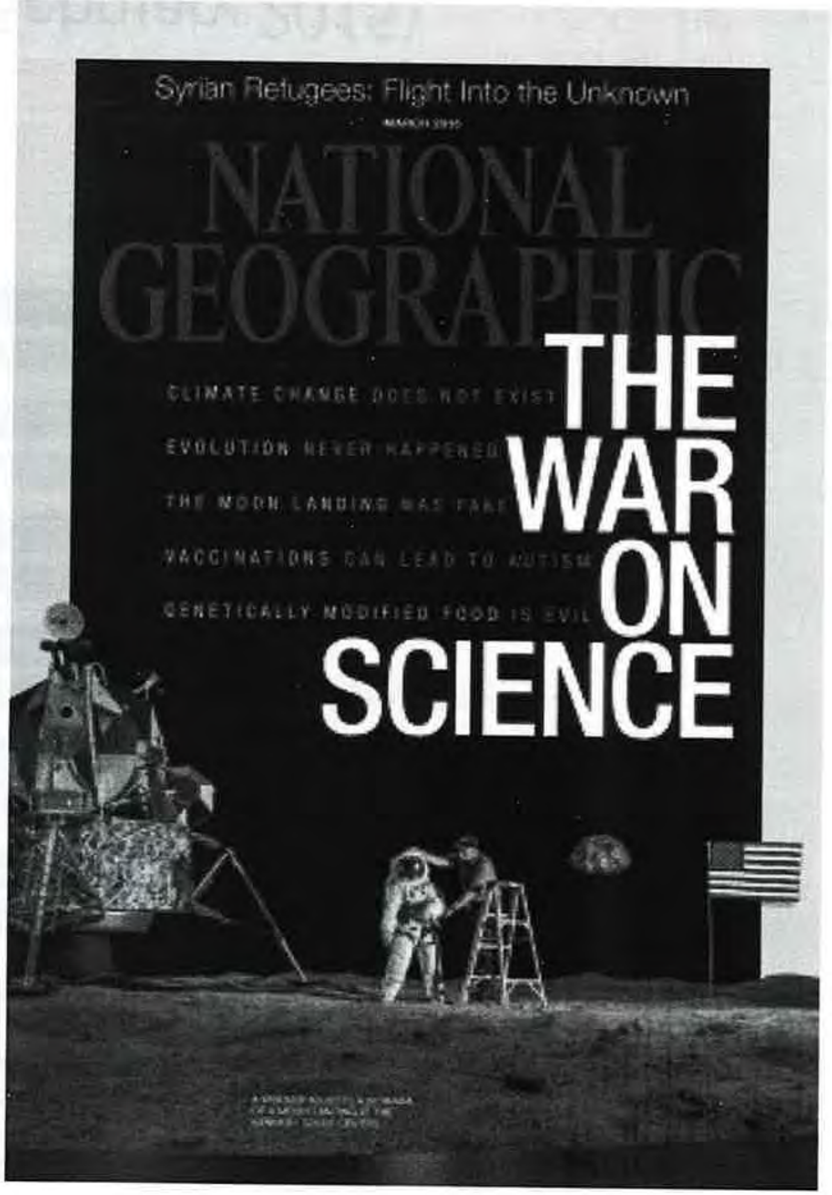
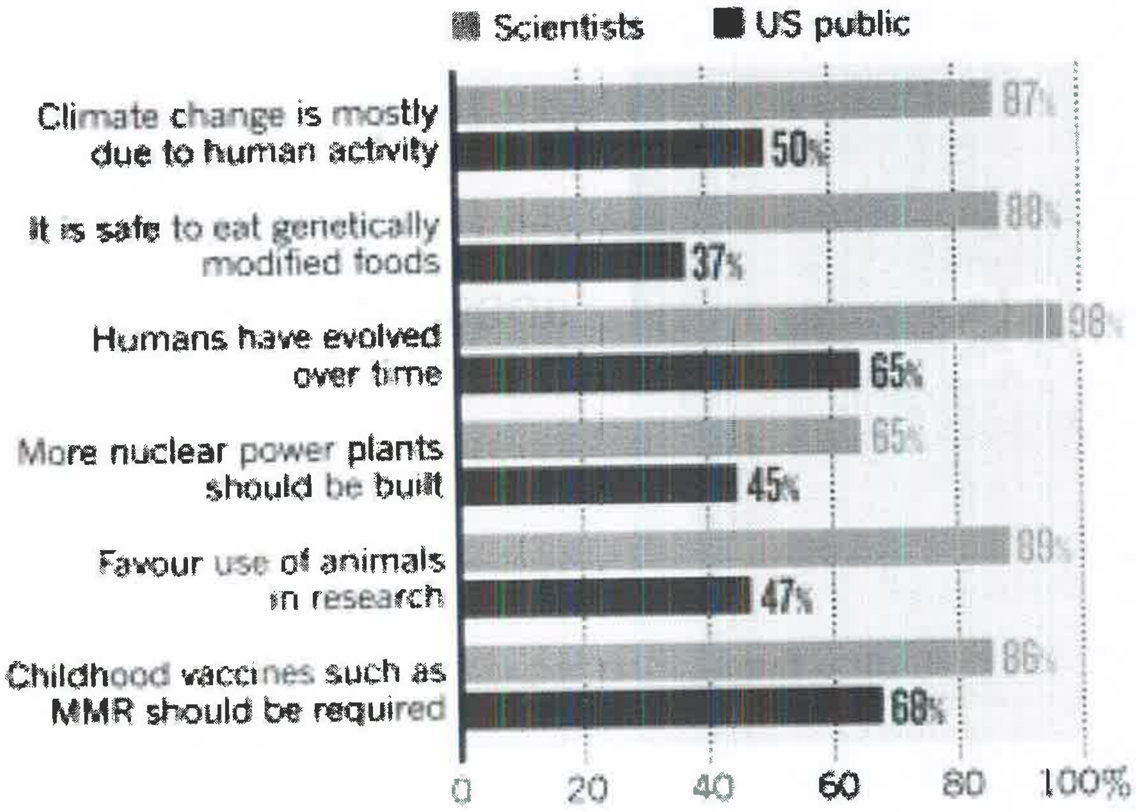
Department of Ecology &
Evolutionary Biology,
University of Colorado



March 2015

OPINION GAP

On hotly debated scientific issues, scientists and the public differ greatly, reveals a poll by the AAAS and Pew Research Center.



Nature 518: 10 (5 February 2015)

Regulation of Genetically Engineered Plants

Within the United States:

- US Department of Agriculture
- US Food and Drug Administration
- US Environmental Protection Agency

Consider the Broader Context

- 1st Principle
  - Do no harm.
    - Human Health
    - The Environment
    - Socio-economically

Benefits should outweigh any costs or harm.

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REVIEW ARTICLE

An overview of the last 10 years of genetically engineered crop safety research

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Abstract

The technology to produce genetically engineered (GE) plants is celebrating its 30th anniversary and one of the major achievements has been the development of GE crops. The safety of GE crops is crucial for their adoption and has been the object of intense research work often ignored in the public debate. We have reviewed the scientific literature on GE crop safety during the last 10 years, built a classified and manageable list of scientific papers, and analyzed the distribution and composition of the published literature. We selected original research papers, reviews, relevant opinions and reports addressing all the major issues that emerged in the debate on GE crops, trying to catch the scientific consensus that has matured since GE plants became widely cultivated worldwide. The scientific research conducted so far has not detected any significant hazards directly connected with the use of GE crops; however, the debate is still intense. An improvement in the efficacy of scientific communication could have a significant impact on the future of agricultural GE. Our collection of scientific records is available to researchers, communicators and teachers at all levels to help create an informed, balanced public perception on the important issue of GE use in agriculture.

Keywords

Biodiversity, environment, feed, food, gene flow, –omics, substantial equivalence, traceability

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Review

Assessment of the health impact of GM plant diets in long-term and multigenerational animal feeding trials: A literature review

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ABSTRACT

The aim of this systematic review was to collect data concerning the effects of diets containing GM maize, potato, soybean, rice, or triticale on animal health. We examined 12 long-term studies (of more than 90 days, up to 2 years in duration) and 12 multigenerational studies (from 2 to 5 generations). We referenced the 90-day studies on GM feed for which long-term or multigenerational study data were available. Many parameters have been examined using biochemical analyses, histological examination of specific organs, hematology and the detection of transgenic DNA. The statistical findings and methods have been considered from each study. Results from all the 24 studies do not suggest any health hazards and, in general, there were no statistically significant differences within parameters observed. However, some small differences were observed, though these fell within the normal variation range of the considered parameter and thus had no biological or toxicological significance. If required, a 90-day feeding study performed in rodents, according to the OECD Test Guideline, is generally considered sufficient in order to evaluate the health effects of GM feed. The studies reviewed present evidence to show that GM plants are nutritionally equivalent to their non-GM counterparts and can be safely used in food and feed.

Prevalence and impacts of genetically engineered feedstuffs on livestock populations[1]

A. L. Van Eenennaam[2] and A. E. Young

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ABSTRACT: Globally, food-producing animals consume 70 to 90% of genetically engineered (GE) crop biomass. This review briefly summarizes the scientific literature on performance and health of animals consuming feed containing GE ingredients and composition of products derived from them. It also discusses the field experience of feeding GE feed sources to commercial livestock populations and summarizes the suppliers of GE and non-GE animal feed in global trade. Numerous experimental studies have consistently revealed that the performance and health of GE-fed animals are comparable with those fed isogenic non-GE crop lines. United States animal agriculture produces over 9 billion food-producing animals annually, and more than 95% of these animals consume feed containing GE ingredients. Data on livestock productivity and health were collated from publicly available sources from 1983, before the introduction of GE crops in 1996, and subsequently through 2011, a period with high levels of predominately GE animal feed. These field data sets, representing over 100 billion animals following the introduction of GE crops, did not reveal unfavorable or perturbed trends in livestock health and productivity. No study has revealed any differences in the nutritional profile of animal products derived from GE-fed animals. Because DNA and protein are normal components of the diet that are digested, there are no detectable or reliably quantifiable traces of GE components in milk, meat, and eggs following consumption of GE feed. Globally, countries that are cultivating GE corn and soy are the major livestock feed exporters. Asynchronous regulatory approvals (i.e., cultivation approvals of GE varieties in exporting countries occurring before food and feed approvals in importing countries) have resulted in trade disruptions. This is likely to be increasingly problematic in the future as there are a large number of "second generation" GE crops with altered output traits for improved livestock feed in the developmental and regulatory pipelines. Additionally, advanced techniques to affect targeted genome modifications are emerging, and it is not clear whether these will be encompassed by the current GE process-based trigger for regulatory oversight. There is a pressing need for international harmonization of both regulatory frameworks for GE crops and governance of advanced breeding techniques to prevent widespread disruptions in international trade of livestock feedstuffs in the future.

Key words: genetic engineering, genetically modified organisms, livestock feed, safety

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In the realm of genetically engineered plants, should keep the principles of **sustainable agriculture** in mind.

Food, Agriculture, Conservation, and Trade Act of 1990

"The term sustainable agriculture means an integrated system of plant and animal production practices having a site-specific application that will, over the long term:

- satisfy human food and fiber needs;
- enhance environmental quality and the natural resource base upon which the agricultural economy depends;
- make the most efficient use of nonrenewable resources and on-farm resources and integrate, where appropriate, natural biological cycles and controls;
- sustain the economic viability of farm operations; and
- enhance the quality of life for farmers and society as a whole."

In the realm of genetically engineered plants, should keep the principles of sustainable agriculture in mind.

What contributes to sustainability for agriculture?

Inputs versus outputs. Long-term target of reducing inputs and increasing output of product.

Inputs

- Seeds or propagules
- Fossil Fuels (till vs. no-till planting)
- Nutrients in the form of fertilizer (fossil fuels)
- Water (fossil fuel?)
- Pesticides (insecticides, miticides, nematicides, ovicides, herbicides, fungicides, antimicrobials for bacteria or viruses, rodenticides) (fossil fuels)

In the realm of genetically engineered plants, should keep the principles of sustainable agriculture in mind.

What contributes to sustainability for agriculture?

Inputs versus outputs. Long-term target of reducing inputs and increasing output of product.

Output dependent on:

- Seeds or propagules (genetic potential)
- Pollination
- Soil quality (water & nutrient holding capacity, salinization, pH)
- Efficiency of water & nutrient acquisition and use
- Losses due to abiotic factors (e.g. H_2O, temperature)
- Losses due to biotic factors (herbivores, pathogens, weeds)

- Herbicide resistance
(corn, sugar beet, alfalfa, soybean, cotton).

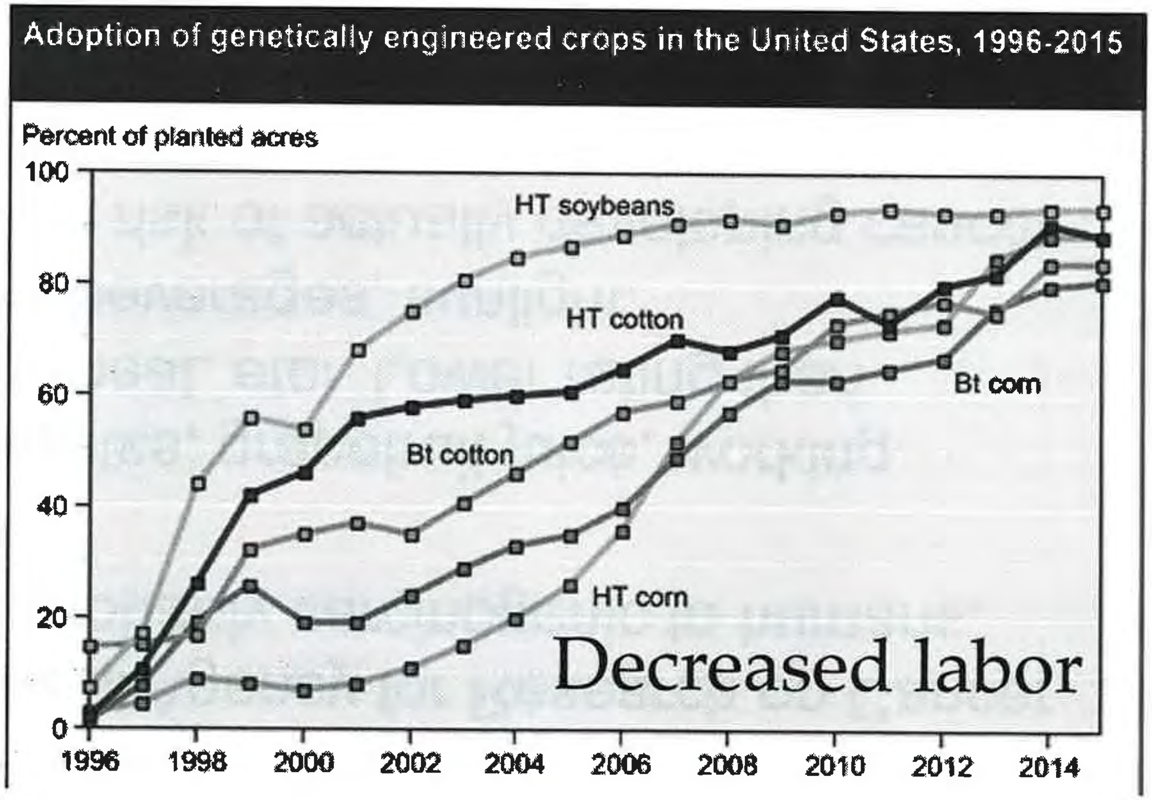
Impact on environment?

Glyphosate (class IV herbicide) is not very toxic, and breaks down quickly.

No-till agricultural practices (better stewardship of land and water).

Reduced fuel consumption and CO_2 emissions (fewer tractor passes over the field, and reduced emission from soil release).

- •Decreased losses due to **pests & pathogens**:


Adoption of genetically engineered crops in the United States, 1996-2015

Decreased labor

http://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us/recent-trends-in-ge-adoption.aspx

Safety of glyphosate (Round-up) herbicide?

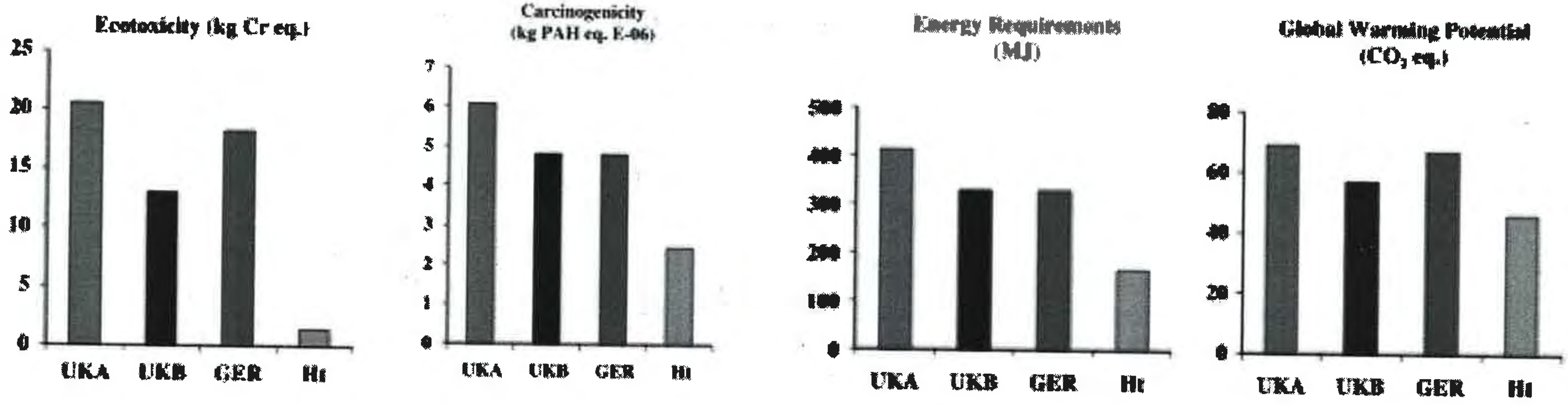
In March 2015, International Agency for Research on Cancer classified glyphosate as probably carcinogenic to humans.

Same classification for apples, grapefruit juice, working the night shift, eating red meat, etc. Lower rating than birth control pill, alcoholic beverages, sunlight. Assessment of hazard, not risk of actually developing cancer.

In November 2015, the European Food Safety Authority, after evaluating more studies than considered by the IARC, concluded that glyphosate is unlikely to be carcinogenic.

- Decreased losses due to **pests & pathogens:**

Herbicide tolerant (Ht) sugar beets



Bennett R, Phipps R, Strange A, Grey P (2004) Environmental and human health impacts of growing genetically modified herbicide-tolerant sugar beet: a life-cycle assessment. *Plant Biotechnology Journal* **2**: 273-278

GM Crops & Food 5:4, 321–332; October/November/December 2014; Published with license by Taylor & Francis Group, LLC

Weed control changes and genetically modified herbicide tolerant crops in the USA 1996–2012

Graham Brookes*

PG Economics; Dorchester; Dorset, UK

Keywords: active ingredient, canola, corn, cotton, glyphosate, herbicide, herbicide tolerant crops, soybeans, sugar beet, weed resistance

Abbreviations: EIQ, environmental impact quotient; GFK, GFK Crop and Animal Health Company; GM, genetically modified; HT, herbicide tolerant; Kg, kilogram; $ US United States dollar; USDA NASS, United States Department of Agriculture National Agricultural Statistics Service

Crops that have been genetically modified (GM) to be tolerant to herbicides have been widely grown in the USA since 1996. The rapid and widespread adoption of this technology reflects the important economic and environmental benefits that farmers have derived from its use (equal to $21.7 billion additional farm income and a 225 million kg reduction in herbicide active ingredient use 1996–2012). During this time, weed control practices in these crops relative to the 'conventional alternative' have evolved to reflect experience of using the technology, the challenges that have arisen and the increasing focus in recent years on developing sustainable production systems. This paper examines the evidence on the changing nature of herbicides used with these crops and in particular how farmers addressed the challenge of weed resistance. The evidence shows that use of the technology has resulted in a net reduction in both the amount of herbicide used and the associated environmental impact, as measured by the EIQ indicator when compared to what can reasonably be expected if the area planted to GM HT crops reverted to conventional production methods. It also facilitated many farmers being able to derive the economic and environmental benefits associated with switching from a plough-based to a no tillage or conservation tillage production system. In terms of herbicide use, the technology has also contributed to a change the profile of herbicides used. A broad range of, mostly selective herbicides has been replaced by one or 2 broad-spectrum herbicides (mostly glyphosate) used in conjunction with one or 2 other (complementary) herbicides. Since the mid-2000s, the average amount of herbicide applied and the associated environmental load, as measured by the EIQ indicator, have increased on both GM HT and conventional crops. A primary reason for these changes has been increasing incidence of weed species developing populations resistant to herbicides and increased awareness of the consequences of relying on a single or very limited number of herbicides for weed control. As a result, growers of GM HT crops have become much more proactive and diversified in their weed management programs in line with weed scientist recommendations and now include other herbicides (with different and complementary modes of action) in combination with glyphosate, even where instances of weed resistance to glyphosate have not been found. The willingness to proactively diversity weed management systems in the GM HT crops is also influenced by a desire to maintain effective weed control and hence continue to enjoy the benefits of no tillage and conservation tillage. Nevertheless, despite the increase in herbicide use in recent years, the use of GM HT technology continues to deliver significant economic and environmental gains to US farmers.

- Decreased losses due to **pests & pathogens:**

8 November 2011

Plant pests:
The biggest threats to food security?

The threat posed to crop production by plant pests and diseases is one the key factors that could lead to "a perfect storm" that threatens to destabilise global food security.

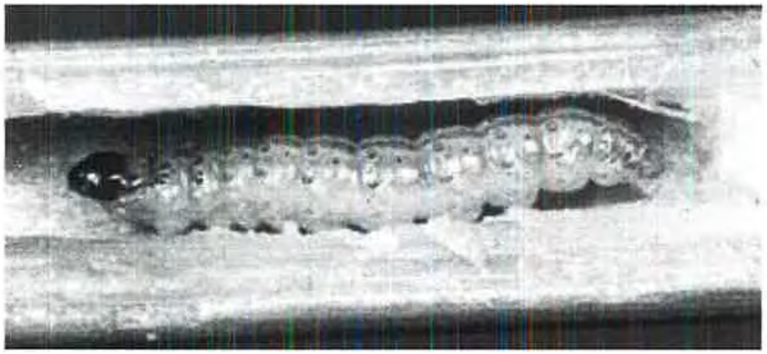
Already, the biological threat accounts for about a 40% loss in global production and the problem is forecast to get worse, scientists warn.

http://www.bbc.co.uk/news/science-environment-15623490

- Decreased losses due to **pests & pathogens**:

-Insects (Bt corn & Bt cotton).

Environment cleaner, safer for farm workers, decreased labor, beneficial organisms spared, decreased fossil fuel use and CO_2 emissions.



http://hgic.clemson.edu/factsheets/Graphics/cornins/borer.htm

http://www.bbc.co.uk/news/science-environment-11496710

Environ. Res. Lett. **10** (2015) 094016 doi:10.1088/1748-9326/10/9/094016

Environmental Research Letters

Benefit to freshwater systems due to decreased ecotoxicity of runoff

LETTER

Changes in environmental impacts of major crops in the US

Yi Yang and Sangwon Suh

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Keywords: agriculture, ecotoxicity, genetically modified organism , pesticide, life cycle assessment

Supplementary material for this article is available online

Abstract

As with life cycle assessment (LCA) studies in general, agricultural LCAs often rely on static and outdated inventory data, but literature suggests that agricultural systems may be highly dynamic. Here, we applied life cycle impact assessment methods to investigate the trends and underlying drivers of changes in non-global environmental impacts of major crops in the US. The results show that the impact per hectare corn and cotton generated on the ecological health of freshwater systems decreased by about 50% in the last decade. This change is mainly due to the use of genetically modified (GM) crops, which has reduced the application of insecticides and relatively toxic herbicides such as atrazine. However, the freshwater ecotoxicity impact per hectare soybean production increased by 3-fold, mainly because the spread of an invasive species, soybean aphid, has resulted in an increasing use of insecticides. In comparison, other impact categories remained relatively stable. By evaluating the relative ecotoxicity potential of a large number of pesticides, our analysis offers new insight into the benefits associated with GM crops. Our study also implies that because different impact categories show different degrees of changes, it is worthwhile focusing on the rapidly changing categories when updating agricultural LCA databases under time and resource constraints.

LETTER

doi:10.1038/nature11153

Widespread adoption of Bt cotton and insecticide decrease promotes biocontrol services

Yanhui Lu[1], Kongming Wu[1], Yuying Jiang[2], Yuyuan Guo[1] & Nicolas Desneux[3]

Over the past 16 years, vast plantings of transgenic crops producing insecticidal proteins from the bacterium *Bacillus thuringiensis* (Bt) have helped to control several major insect pests[1–5] and reduce the need for insecticide sprays[1,5,6]. Because broad-spectrum insecticides kill arthropod natural enemies that provide biological control of pests, the decrease in use of insecticide sprays associated with Bt crops could enhance biocontrol services[7–12]. However, this hypothesis has not been tested in terms of long-term landscape-level impacts[10]. On the basis of data from 1990 to 2010 at 36 sites in six provinces of northern China, we show here a marked increase in abundance of three types of generalist arthropod predators (ladybirds, lacewings and spiders) and a decreased abundance of aphid pests associated with widespread adoption of Bt cotton and reduced insecticide sprays in this crop. We also found evidence that the predators might provide additional biocontrol services spilling over from Bt cotton fields onto neighbouring crops (maize, peanut and soybean). Our work extends results from general studies evaluating ecological effects of Bt crops[1–4,6,12,13] by demonstrating that such crops can promote biocontrol services in agricultural landscapes.

Nature (2012) 487: 362-365

Areawide Suppression of European Corn Borer with Bt Maize Reaps Savings to Non-Bt Maize Growers

W. D. Hutchison,[1]* E. C. Burkness,[1] P. D. Mitchell,[2] R. D. Moon,[1] T. W. Leslie,[3] S. J. Fleischer,[4] M. Abrahamson,[5] K. L. Hamilton,[6] K. L. Steffey,[7]† M. E. Gray,[7] R. L. Hellmich,[8] L. V. Kaster,[9] T. E. Hunt,[10] R. J. Wright,[11] K. Pecinovsky,[12] T. L. Rabaey,[13] B. R. Flood,[14] E. S. Raun[15]‡

Transgenic maize engineered to express insecticidal proteins from the bacterium *Bacillus thuringiensis* (Bt) has become widely adopted in U.S. agriculture. In 2009, Bt maize was planted on more than 22.2 million hectares, constituting 63% of the U.S. crop. Using statistical analysis of per capita growth rate estimates, we found that areawide suppression of the primary pest *Ostrinia nubilalis* (European corn borer) is associated with Bt maize use. Cumulative benefits over 14 years are an estimated \$3.2 billion for maize growers in Illinois, Minnesota, and Wisconsin, with more than \$2.4 billion of this total accruing to non-Bt maize growers. Comparable estimates for Iowa and Nebraska are \$3.6 billion in total, with \$1.9 billion for non-Bt maize growers. These results affirm theoretical predictions of pest population suppression and highlight economic incentives for growers to maintain non-Bt maize refugia for sustainable insect resistance management.

Science (2010) 330: 222-225

Even the Amish, who are averse to anything technological, have embraced the growing of Bt corn.

http://www.biofortified.org/2013/10/amish-gmos/

A Meta-Analysis of the Impacts of Genetically Modified Crops

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Abstract

Background: Despite the rapid adoption of genetically modified (GM) crops by farmers in many countries, controversies about this technology continue. Uncertainty about GM crop impacts is one reason for widespread public suspicion.

Objective: We carry out a meta-analysis of the agronomic and economic impacts of GM crops to consolidate the evidence.

Data Sources: Original studies for inclusion were identified through keyword searches in ISI Web of Knowledge, Google Scholar, EconLit, and AgEcon Search.

Study Eligibility Criteria: Studies were included when they build on primary data from farm surveys or field trials anywhere in the world, and when they report impacts of GM soybean, maize, or cotton on crop yields, pesticide use, and/or farmer profits. In total, 147 original studies were included.

Synthesis Methods: Analysis of mean impacts and meta-regressions to examine factors that influence outcomes.

Results: On average, GM technology adoption has reduced chemical pesticide use by 37%, increased crop yields by 22%, and increased farmer profits by 68%. Yield gains and pesticide reductions are larger for insect-resistant crops than for herbicide-tolerant crops. Yield and profit gains are higher in developing countries than in developed countries.

Limitations: Several of the original studies did not report sample sizes and measures of variance.

Conclusion: The meta-analysis reveals robust evidence of GM crop benefits for farmers in developed and developing countries. Such evidence may help to gradually increase public trust in this technology.

Citation: Klümper W, Qaim M (2014) A Meta-Analysis of the Impacts of Genetically Modified Crops. PLoS ONE 9(11): e111629. doi:10.1371/journal.pone.0111629

Key global economic and environmental impacts

of genetically modified (GM) crop use 1996-2012

KEYWORDS: yield, cost, income, production, genetically modified crops, pesticide, carbon sequestration, no tillage, environmental impact quotient

Abstract This paper summarises the economic and key environmental impacts that crop biotechnology has had on global agriculture. The analysis shows that there have been very significant net economic benefits at the farm level amounting tc $18.8 billion in 2012 and $116.6 billion for the seventeen year period 1996-2012 (in nominal terms). These economic gains have been divided roughly 50 percent each to farmers in developed and developing countries. GM technology have also made important contributions to increasing global production levels of the four main crops, having added 122 million tonnes and 230 million tonnes respectively, to the global production of soybeans and maize since the introduction of the technology in the mid-1990s. In terms of key environmental impacts, the adoption of the technology has reduced pesticide spraying by 503 million kg (-8.8 percent) and, as a result, decreased the environmental impact associated with herbicide and insecticide use on these crops (as measured by the indicator the Environmental Impact Quotient (EIQ)) by18.7 percent. The technology has also facilitated a significant reduction in the release of greenhouse gas emissions from this cropping area, which, in 2012, was equivalent to removing 11.88 million cars from the roads.

Agro Food Industry Hi Tech (2014) 25: 43-47

Fatal attraction: the intuitive appeal of GMO opposition

Stefaan Blancke[1], Frank Van Breusegem[2,3], Geert De Jaeger[2,3], Johan Braeckman[1], and Marc Van Montagu[2,3,4]

[1] Department of Philosophy and Moral Sciences, Ghent University, 9000 Ghent, Belgium
[2] Department of Plant Systems Biology, VIB, 9052 Ghent, Belgium
[3] Department of Plant Biotechnology and Bioinformatics, Ghent University, 9052 Ghent, Belgium
[4] Institute of Plant Biotechnology Outreach–VIB, Incubation and Innovation Center, Ghent University, 9052 Ghent, Belgium

Public opposition to genetically modified organisms (GMOs) remains strong. By contrast, studies demonstrate again and again that GM crops make a valuable contribution to the development of a sustainable type of agriculture. The discrepancy between public opinion and the scientific evidence requires an explanation. We argue that intuitive expectations about the world render the human mind vulnerable to particular misrepresentations of GMOs. We explain how the involvement of particular intuitions accounts for the popularity, persistence, and typical features of GM opposition and tackle possible objections to our approach. To conclude, we discuss the implications for science education, science communication, and the environmental movement.

Trends in Plant Science (2015) 20: 414-418

Comparing the yields of organic and conventional agriculture

Verena Seufert[1], Navin Ramankutty[1] & Jonathan A. Foley[2]

Numerous reports have emphasized the need for major changes in the global food system: agriculture must meet the twin challenge of feeding a growing population, with rising demand for meat and high-calorie diets, while simultaneously minimizing its global environmental impacts[1,2]. Organic farming—a system aimed at producing food with minimal harm to ecosystems, animals or humans—is often proposed as a solution[3,4]. However, critics argue that organic agriculture may have lower yields and would therefore need more land to produce the same amount of food as conventional farms, resulting in more widespread deforestation and biodiversity loss, and thus undermining the environmental benefits of organic practices[5]. Here we use a comprehensive meta-analysis to examine the relative yield performance of organic and conventional farming systems globally. Our analysis of available data shows that, overall, organic yields are typically lower than conventional yields. But these yield differences are highly contextual, depending on system and site characteristics, and range from 5% lower organic yields (rain-fed legumes and perennials on weak-acidic to weak-alkaline soils), 13% lower yields (when best organic practices are used), to 34% lower yields (when the conventional and organic systems are most comparable). Under certain conditions—that is, with good management practices, particular crop types and growing conditions—organic systems can thus nearly match conventional yields, whereas under others it at present cannot. To establish organic agriculture as an important tool in sustainable food production, the factors limiting organic yields need to be more fully understood, alongside assessments of the many social, environmental and economic benefits of organic farming systems.

Nature (2012) 485: 229-234

Lower yields for organic

Tilling and hoeing are primary techniques to eliminate weeds – leads to soil erosion, lower water-holding capacity, and loss of nutrients.

Major food-borne illness outbreaks have been associated with organic practices

http://en.wikipedia.org/wiki/2011_Germany_E._coli_O104:H4_outbreak

UC Sustainable Agriculture Research and Education Program

http://www.sarep.ucdavis.edu/concept.htm

“Sustainable agriculture integrates three main goals--environmental health, economic profitability, and social and economic equity.”

“Sustainability rests on the principle that we must meet the needs of the present without compromising the ability of future generations to meet their own needs. Therefore, stewardship of both natural and human resources is of prime importance.”

I see no justification for limiting the farmer’s utilization of completely legal agricultural practices that, based on the evidence, represent a more sustainable approach to farming.

Cropland Policy Mtg
2/9/2016
Steven Hoffman

THE WALL STREET JOURNAL.
WSJ.com

May 22, 2014, 2:50 PM ET

Can Organic Farming Counteract Carbon Emissions?

ByRani Molla

Organic practices could counteract the world's yearly carbon dioxide output while producing the same amount of food as conventional farming, a new study suggests.

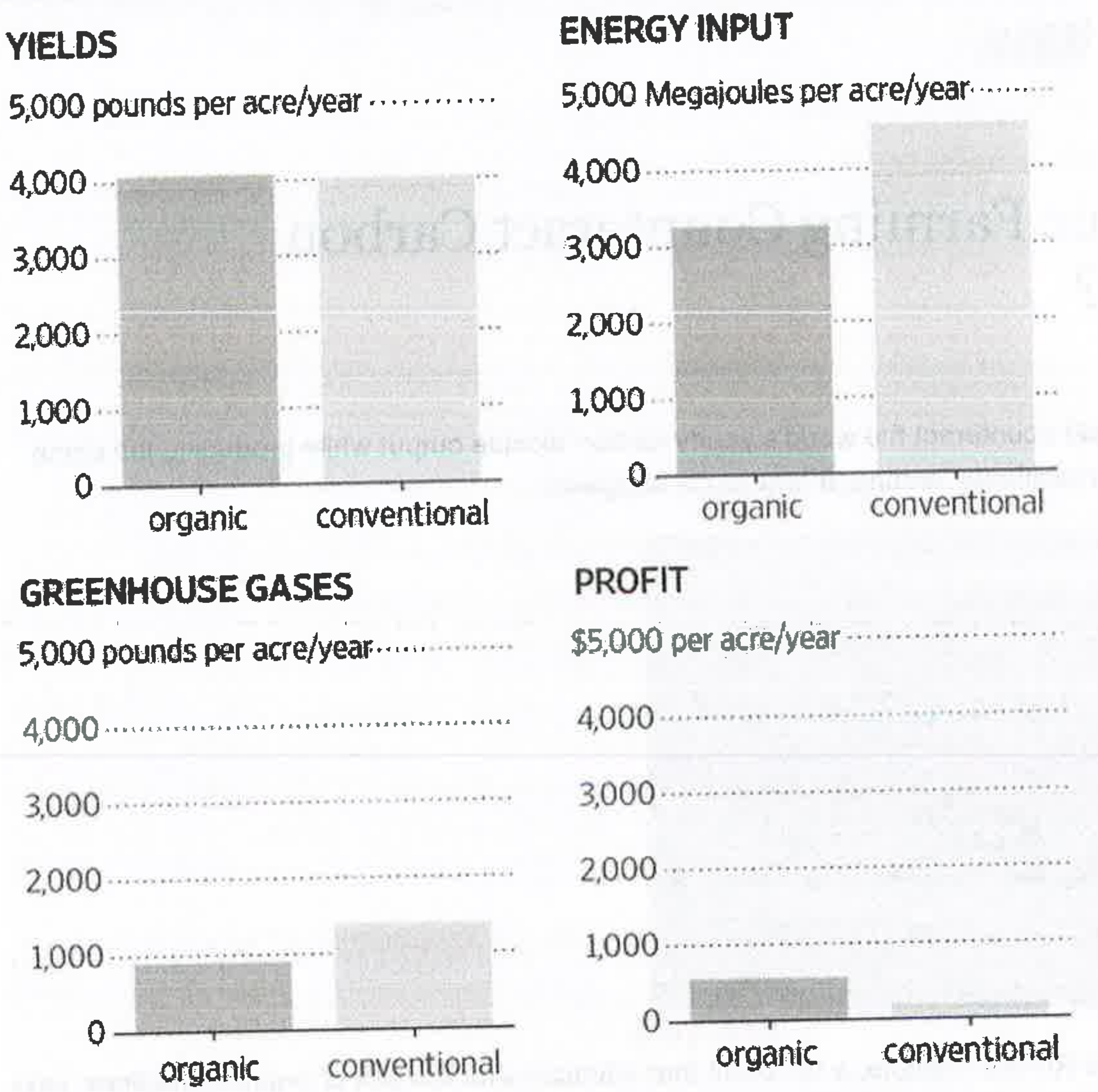
Bloomberg News

The white paper by the Rodale Institute, a nonprofit that advocates for the use of organic practices, says that using "regenerative organic agriculture," such as low or no-tillage, cover crops and crop rotation, will keep photosynthesized carbon dioxide in the soil instead of returning it to the atmosphere.

Citing 75 studies from peer-reviewed journals, including its own 33-year Farm Systems Trial, Rodale Institute concluded that if all cropland were converted to the regenerative model it would sequester 40% of annual CO2 emissions; changing global pastures to that model would add another 71%, effectively overcompensating for the world's yearly carbon dioxide emissions.

Michel Cavigelli, a research soil scientist at the USDA's Agricultural Research Service, which has a slightly different 19-year side-by side study, says his research also shows that organic soil has higher carbon content than conventional but warns that the devil is in the details. For example, the USDA study tills the organic plot and that might cause the manure's carbon to stay deeper in the soil.

But the question organic farming always comes back to is whether farming without synthetic pesticides and genetically modified organisms is really a viable way to feed the planet. Rodale Institute believes it can do that and better.



Seed By Side

How organic and conventional farming compare over 30 years

YIELDS

ENERGY INPUT

GREENHOUSE GASES

PROFIT

Rodale Institute

Rani Molla/The Wall Street Journal

In the longest-running study of its kind, Rodale's Farming Systems Trial compares organic farming with conventional farming, by farming neighboring plots just as organic farmers and traditional farmers would — that means its organic farming plot utilizes techniques like crop rotation and cover crops while the conventional plot uses common synthetic pesticides and genetically modified organisms. Both organic and conventional fields were divided into tilled and no-till areas to reflect that farmers use both practices.

The findings show that organic farming yields are lower than conventional in the first few years, while conventional crops do better in the first years than they do later on. Over time the production equals out and with organic outperforming conventional farming production in years of drought (organic corn yields 31% more than conventional corn during drought).

"When you start to grow using organic methods and products, the soil is still depleted," Executive

Director Coach Mark Smallwood said. “That's why the yield initially isn't as high.” He says that organic farming betters the soil over time, while conventional farming depletes it. “If the soil is weak, so too will be the plants,” he said.

Additionally, the study shows that organic farming requires less energy and emits less greenhouse gas. Paired with higher price points at market, the study shows organic produce to be more profitable.

Mr. Cavigelli says that organic crops in his study yield 80% of what conventional yields, in contrast to the Rodale study that showed similar yields. The difference, he says, is that while the organics show similar yields to the Rodale study, the conventional crops have higher yields, perhaps due to different conventional farming techniques.

“There's a whole bunch of ways to do organic and conventional farming,” Mr. Cavigelli said. “You can find different results based on details of how the management is done.”

According to Steve Savage, a Stanford- trained biologist and organic critic who consults for the agriculture industry, “There's nothing wrong in principal [with the organic production findings] but in general there are the practical aspects of this being scaled up.” He sites issues such as attaining enough cow manure and that many farmers rent their land, which disincentives efforts to build up the soil.

Cropland Policy Mtg
2/9/2016

Steven Hoffman

Study: Monsanto's Glyphosate Most Heavily Used Weed-Killer in History | EWG

Nearly 75 Percent of All Glyphosate Sprayed on Crops Came in the Last 10 Years; Surging Use in both U.S. and Globally Raises New Concerns for Health and the Environment

Contact: Shannon Van Hoesen(202) 667-6982
shannon@ewg.org
FOR IMMEDIATE RELEASE: TUESDAY, FEBRUARY 2, 2016

WASHINGTON – Monsanto's signature herbicide glyphosate, first marketed as "Roundup," is now the most widely and heavily applied weed-killer in the history of chemical agriculture in both the U.S. and globally, according to **a landmark report published today**.

The paper, published Feb. 2, 2016 in the peer-reviewed journal Environmental Sciences Europe, reports that to date 18.9 billion pounds (8.6 billion kilograms) of glyphosate have been used globally. Glyphosate use has risen almost 15-fold since so-called "Roundup Ready" genetically engineered crops were introduced in 1996.

In 2014, enough glyphosate was sprayed to leave more than three-quarters of a pound of the active ingredient on every harvested acre of cropland in the U.S., and remarkably, almost a half pound per acre on all cropland worldwide (0.53 kilogram/hectare).

The paper by Charles Benbrook, Ph.D., titled "Trends in glyphosate herbicide use in the United States and Globally," is available free online at **Environmental Sciences Europe**.

"The dramatic and rapid growth in overall use of glyphosate will likely contribute to a host of adverse environmental and public health consequences," Dr. Benbrook wrote.

Last year, 17 of the world's top cancer researchers voted unanimously to elevate glyphosate's cancer profile on behalf of the World Health Organization. After the panel of experts reviewed all of the publicly available research, the WHO's International Agency for Research on Cancer (IARC) classified the weed-killer as "probably carcinogenic to humans." Following WHO's action, the state of California is currently in the process of listing glyphosate as a known human carcinogen under its Proposition 65 law.

As Benbrook's paper notes, other recent studies have found connections between glyphosate exposure and a number of other serious health effects, including liver and kidney damage and non-Hodgkin lymphoma, among others.

Remarkably, 74 percent of all glyphosate sprayed on crops since the mid-1970s was applied in just the last 10 years, as cultivation of genetically engineered corn and soybean crops exploded on both U.S. and global croplands.

Glyphosate was first sold commercially in 1974, but its use by farmers was limited at first because the active ingredient killed both weeds and crops. The subsequent development and approval of genetically engineered (GE), herbicide-tolerant (HT) crops dramatically changed how farmers could apply it. Starting in 1996, Monsanto and other seed companies began marketing GE-HT versions of three major crops – cotton, corn, and soybeans –making it possible for farmers to apply glyphosate for months after crops started growing.

The use and efficacy of HT technology, particularly in its first decade, led to its rapid and near-universal adoption in the U.S., Canada, Argentina, Brazil, and a half-dozen other countries. As a result, glyphosate use by U.S. farmers rose from 12.5 million pounds in 1995 to 250 million pounds in 2014, a 20-fold increase. Globally, total use rose from 112.6 million pounds in 1995 to 1.65 billion in 2014, a nearly 15-fold jump.

"My hope is that this paper will stimulate more research on glyphosate use and human and environmental exposure patterns to increase the chance that scientists will quickly detect any problems that might be triggered, or made worse, by glyphosate exposure," Benbrook added.

"This report makes it clear that the use of glyphosate, combined with the dominance of genetically engineered crops, has produced a looming public health threat both in the U.S. and around the world," said Mary Ellen Kustin, senior policy analyst at EWG. "Farmers have sprayed billions of pounds of a chemical now considered a probable human carcinogen over the past decade. Growers spray glyphosate several times a year on the majority of U.S. cropland. The sheer volume of use of this toxic weed-killer is a clear indication that this chemical dependency is a case of farming gone wrong."

This is the second paper by Benbrook published in Environmental Sciences Europe. The first, "Impacts of genetically engineered crops on pesticide use in the U.S. – the first sixteen years," was published in September 2012 and remains the most heavily accessed paper in the 25-year history of the journal, with more than 230,000 views.

###

References: Benbrook, C. Trends in glyphosate herbicide use in the United States and globally. *Environmental Sciences Europe* (2016, 28:28) doi:10.1186/s12302-016-0070-0. Access full text at: **http://www.enveurope.com/content/28/1/3**

Benbrook, C. "Impacts of genetically engineered crops on pesticide use in the U.S. – the first sixteen years." *Environmental Sciences Europe* (2012, Vol. 24:24. doi:10.1186/2190-4715-24-24. Access full text at: http://www.enveurope.com/content/24/1/24

Both reports are part of Springer's open access publishing portfolio, SpringerOpen, and is available free online.

KEY ISSUES: PESTICIDES FARMING CHEMICALS IN FOOD GMO FOODS

Cropland Policy Mtg.
2/9/2016
Steven Hoffman

5.5 Myth: GM has enabled the adoption of environmentally friendly no-till farming

Truth: GM has had little impact on the adoption of no-till farming, and no-till with GM herbicide-tolerant crops is not environmentally friendly

Myth at a glance

GMO proponents claim that GM herbicide-tolerant crops, notably GM Roundup Ready (RR) crops, are environmentally friendly because they allow farmers to adopt the no-till system of cultivation. No-till farming avoids ploughing in order to conserve soil and water. It is claimed to reduce carbon dioxide emissions by sequestering more carbon in the soil.

In no-till cultivation of GM herbicide-tolerant crops, farmers try to control weeds through herbicide applications rather than mechanically, by ploughing.

However, USDA data show that the introduction of GM crops did not significantly increase no-till adoption.

A study comparing the environmental impact of GM RR and non-GM soy found that once the ecological damage caused by herbicides is taken into account, the negative environmental impact of GM soy is greater than that of non-GM soy in both no-till and tillage systems. Also, the adoption of no-till raised the negative environmental impact level, whether the soy was GM RR or non-GM.

No-till fields do not sequester more carbon than ploughed fields when carbon sequestration at soil depths greater than 30 cm is taken into account.

Claims of environmental benefits from no-till herbicide-tolerant farming systems are unjustified.

GMO proponents claim that GM herbicide-tolerant crops, notably GM Roundup Ready (RR) crops, are environmentally friendly because they allow farmers to adopt the no-till system of cultivation. No-till farming avoids ploughing in order to conserve soil and water. It is claimed to reduce carbon dioxide emissions by sequestering more carbon in the soil.

In no-till cultivation of GM herbicide-tolerant crops, farmers try to control weeds through herbicide applications rather than mechanically, by ploughing.

There are several problems with the inflated claims made for the environmental benefits of this farming system, which are detailed below.

GM is not needed to practise no-till

No-till or low-till farming can be – and is – practised in chemically-based non-GM and agroecological farming. Farmers do not have to adopt GM crops or use herbicides to practise no-till.

GM has not significantly increased the adoption of no-till

The vast majority of no-till and low-till adoption in the US occurred before GM crops came onto the market and rates of adoption have stagnated since, according to a US Department of Agriculture report. The report says that adoption of no-till and low-till for soybeans grew from 25% of the soybean acreage in 1990 to 48% in 1995, the 5-year period previous to the introduction of GM herbicide-tolerant soybeans. Growth of no-till and low-till increased further in 1996, the year herbicide-tolerant soybeans were introduced, but then stagnated to 50–60% in the following years.[1]

Biotechnology expert Dr Doug Gurian-Sherman of the Union of Concerned Scientists commented on the findings: "Roundup Ready crops have made no-till easier, but so have no-till seed drills, and Farm Bill incentives that went into effect in 1986. If you actually look at the additional adoption of no-till after 1996, it is only a few per cent in corn, almost nothing in cotton, and a little more in soy (maybe 5 to 10% of acres). So contrary to the widespread myth, the data do not support a major role of GM crops in the increase in no-till over the past few decades."[2]

Claims of environmental benefits for no-till with GM are misleading

Claims of environmental benefits for GM herbicide-tolerant crops with no-till cultivation are misleading. One study compared the environmental impacts of growing GM RR and non-GM soy, using an indicator called Environmental Impact Quotient (EIQ). EIQ assesses the negative environmental impacts of the use of pesticides and herbicides on farm workers, consumers and ecology (fish, birds, bees and other beneficial insects).

The study found that in Argentina, the negative environmental impact of GM soy was higher than that of non-GM soy in both no-till and tillage systems, because of the herbicides used. These are broad-spectrum in nature – that is, they kill all plants except GM plants engineered to tolerate them. Also, the adoption of no-till raised the EIQ, whether the soy was GM RR or non-GM. The main reason for the increase in herbicides used in no-till systems was the spread of glyphosate-resistant superweeds.[3]

The spread of herbicide-resistant superweeds has undermined the GM no-till model of farming, forcing farmers back to ploughing and even pulling weeds by hand.[4]

No-till farming does not sequester more carbon

Chemically-based agriculture is a major contributor to climate change, producing over 20% of greenhouse gas emissions.[5] GMO proponents claim that soil in no-till systems sequesters (stores) more carbon than ploughed soil, preventing the carbon from being released into the atmosphere as the greenhouse gas carbon dioxide and thus helping to mitigate climate change.

However, a comprehensive review of the scientific literature found that no-till fields sequester no more carbon than ploughed fields when carbon sequestration at soil depths greater than 30 cm is taken into account. Studies claiming to find carbon sequestration benefits from no-till only measure carbon sequestration down to a depth of about 30 cm and so do not give an accurate picture.[6]

Conclusion

Claims of environmental benefits from no-till farming with GM crops are misleading and unjustified. No-till farming can be and is practised by chemically-based non-GM and agroecological growers and it is not necessary to grow GM crops to practise it. The introduction of GM crops has not significantly increased no-till adoption.

No-till farming with GM herbicide-tolerant crops is not environmentally friendly. A study carried out in Argentina found that the negative environmental impact of GM soy was higher than that of non-GM soy in both no-till and tillage systems, because of the herbicides used. No-till fields also do not sequester more carbon than ploughed fields when soil depths greater than 30 cm are taken into account.

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The Organic Center | Organic agriculture as a solution to climate change

Organic agriculture as a solution to climate change

Feb 03, 2016

Photo credit: Timothy Swinson

We've all heard about the effects that climate change is having on our Earth: hotter temperatures, sea level rises that threaten to gobble up our coast lines, and more severe weather events including droughts and flooding. The consequences are dire, but what can we as individuals do to remedy the situation? Should we give up our cars or vow to never set foot on a plane again? Luckily, combating climate change can be as simple as supporting organic agriculture. Numerous studies have demonstrated how switching from conventional to organic farming methods can decrease the amount of carbon in the atmosphere, and reduce greenhouse gas emissions and energy usage all while increasing our food security.

Photo credit: Mikael Miettinen

One of the primary ways in which humans contribute to global warming is by releasing the greenhouse gas carbon dioxide (CO_2) into the atmosphere by burning fossil fuels such as gas or oil. For example, every time we drive our cars, we release CO_2 into the atmosphere. As the amount of CO_2 in the atmosphere increases, so will the severity of climate change. One way to reduce atmospheric CO_2 and combat global warming is by transferring the carbon from the atmosphere onto the Earth's surface. Soil contains more carbon than all of the air and forests in the world, and it also happens to be one of the easiest places to deposit carbon from greenhouse gasses.

Photo Credit: Dwight Sipler

According to a study published in the journal *Science*, we could remove up to 78 Gt (78,000,000,000 tons) of carbon from the atmosphere simply by rejuvenating soils that have been depleted of carbon by conventional farming methods. That's enough to offset up to 15% of the entire world's fossil fuel emissions. A study published in the *Proceedings of the National Academy of the Sciences*, determined that organic farming is an effective way to simultaneously restore carbon to our soils and reduce carbon in the atmosphere. Furthermore, a 30-year study comparing organic and conventional farming methods conducted by the Rodale Institute found that soils farmed using organic methods were healthier and continued to experience an increase in carbon-based organic matter over time. On the other hand, soils farmed using conventional methods saw reductions in soil carbon and nutrients.


Photo credit: Chafer 33

Organic agriculture also leaves a much smaller environmental footprint than conventional agriculture. Research published in *Current Agriculture Research Journal* and by the Rodale Institute found that organic farming methods release significantly fewer greenhouse gasses and use less energy than conventional farming methods. Conventional farming relies heavily on the use of chemical fertilizers, herbicides, and pesticides. The synthesis, transport and application of these chemicals are very energy intensive. The Farm System Trials by the Rodale Institute found a 45% increase in energy use with conventional farming methods when compared to organic methods. Greenhouse gas emissions were 40% lower in organic farm systems than in conventional farming systems due to a combination of reduced need for fossil fuels and lower N_2O emissions.

Have you ever noticed that during some years, produce is more expensive than it is in other years? Oftentimes this is because bad weather has destroyed crops, leading to a lower yield and forcing farmers to charge you more to make up for their losses. Climate change is ushering in a new era of climate extremes including severe droughts and heavy rains. According to the *United States Global Change Research Project*, farmers are already experiencing a decline in agricultural yields due to extreme weather events.

In a study comparing organic and conventional systems researchers found that organic farmlands performed better during droughts by capturing and storing water more efficiently than conventional farms. These same fields also outperformed the conventionally farmed fields during heavy rainstorms because they experienced less runoff and erosion. In a world where a more volatile climate is becoming the norm, organic agriculture is more resilient, ensuring greater food security than conventional agriculture. As Steve Hoffman from Compass Natural and Regeneration International says in his blog *Organic, Regenerative Agriculture a Low-Cost Solution to Climate Change*,"It seems like a powerful solution to climate change lies literally right under our feet."

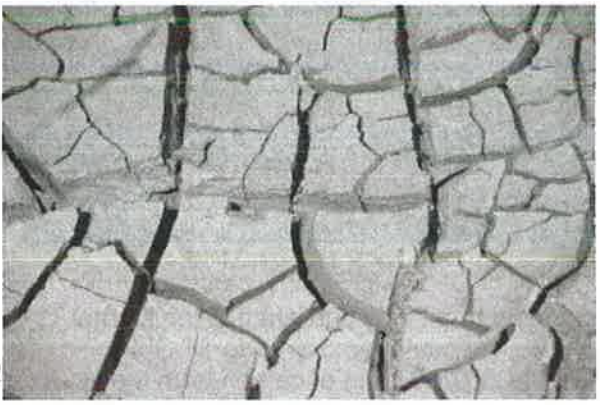
Photo credit: Max Wolfe

To find out more about how organic agriculture can provide a solution to climate change, check out the panel discussion "Organic & Carbon: The Climate Change Connection"—which includes The Organic Center's Science Advisory Board Member Dr. Kathleen Delate—at Natural Products Expo West this March.

Session Details

Date: Thursday, March 10, 2016

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Organic agriculture key to feeding the world sustainably | College of Agricultural, Human, and Natural Resource Sciences | Washington State University

FEBRUARY 3, 2016

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Organic agriculture key to feeding the world sustainably


John Reganold, Regents Professor of Soil Science & Agroecology

PULLMAN, Wash.—Washington State University researchers have concluded that feeding a growing global population with sustainability goals in mind is possible. Their review of hundreds of published studies provides evidence that organic farming can produce sufficient yields, be profitable for farmers, protect and improve the environment and be safer for farm workers.

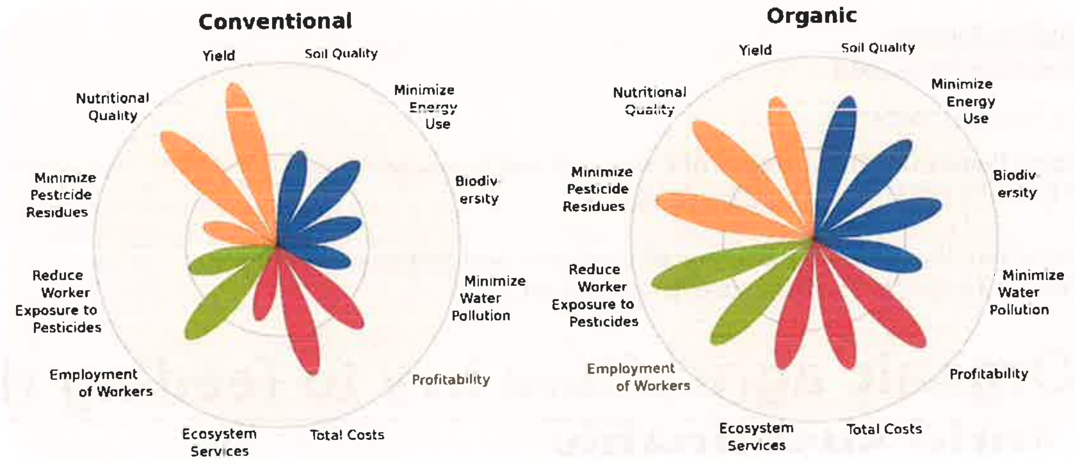
The review study, “Organic Agriculture in the 21st Century,” is featured as the cover story for February issue of the journal Nature Plants and was authored by John Reganold, WSU regents professor of soil science and agroecology and doctoral candidate Jonathan Wachter. It is the first such study to analyze 40 years of science comparing organic and conventional agriculture across the four goals of sustainability identified by the National Academy of Sciences: productivity, economics, environment, and community well being.

“Hundreds of scientific studies now show that organic ag should play a role in feeding the world” said Reganold, lead author of the study. “Thirty years ago, there were just a couple handfuls of studies comparing organic agriculture with conventional. In the last 15 years, these kinds of studies have skyrocketed.”

Organic production currently accounts for only one percent of global agricultural land, despite rapid growth in the last two decades.

Critics have long argued that organic agriculture is inefficient, requiring more land to yield the same amount of food. The review paper describes cases where organic yields can be higher than conventional farming methods.

"In severe drought conditions, which are expected to increase with climate change, organic farms have the potential to produce high yields because of the higher water-holding capacity of organically farmed soils," Reganold said.



An assessment of organic farming relative to conventional farming illustrates that organic systems better balance the four areas of sustainability (Reganold and Wachter, 2016).

However, even when yields may be lower, organic agriculture is more profitable for farmers because consumers are willing to pay more. Higher prices can be justified as a way to compensate farmers for providing ecosystem services and avoiding environmental damage or external costs.

Numerous studies in the review also prove the environmental benefits of organic production. Overall, organic farms tend to store more soil carbon, have better soil quality, and reduce soil erosion. Organic agriculture also creates less soil and water pollution and lower greenhouse gas emissions. And it's more energy efficient because it doesn't rely on synthetic fertilizers or pesticides. It is also associated with greater biodiversity of plants, animals, insects and microbes as well as genetic diversity. Biodiversity increases the services that nature provides like pollination and improves the ability of farming systems to adapt to changing conditions.

Reganold said that feeding the world is not only a matter of yield but also requires examining food waste and the distribution of food.

"If you look at calorie production per capita we're producing more than enough food for 7 billion people now, but we waste 30 to 40 percent of it," Reganold said. "It's not just a matter of producing enough, but making agriculture environmentally friendly and making sure that food gets to those who need it."

Reganold and Wachter suggest that no single type of farming can feed the world. Rather, what's needed is a balance of systems, "a blend of organic and other innovative farming systems, including agroforestry, integrated farming, conservation agriculture, mixed crop/livestock and still undiscovered systems."

Reganold and Wachter recommend policy changes to address the barriers that hinder the expansion of organic agriculture. Such hurdles include the costs of transitioning to organic certification, lack of access to labor and markets, and lack of appropriate infrastructure for storing and transporting food. Legal and financial tools are necessary to encourage the adoption of innovative, sustainable farming practices.

Citation: Reganold, John P. and Jonathan M. Wachter. Organic agriculture in the twenty-first century. *Nature Plants*. Vol. 2 (2016) DOI: 10.1038/NPLANTS.2015.221.

http://css.wsu.edu/people/faculty/john-p-reganold

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Scientists Discover Key Molecule Linking Neonicotinoids to Honey Bee Viruses

Beyond Pesticides |October 24, 2013 12:59 pm | Comments

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A team of scientists in Italy believe they have found the molecular mechanism through which neonicotinoid pesticides adversely impacts the immune system of honey bees. The team's experiments suggest that exposure to neonicotinoids results in increased levels of a particular protein in bees that inhibits a key molecule involved in the immune response, making the insects more susceptible to attack by harmful viruses.

Neonicotinoids cause significant problems for honey bees, include disruptions in mobility, navigation, feeding behavior, foraging activity, memory and learning, and overall hive activity.

Though previous studies have indicated that exposure to minute amount of neurotoxic pesticides like neonicotinoids severely impair the immune systems of bees, making them more susceptible to pathogens, the underlying mechanism has was not yet fully understood. The study, published in the *Proceedings of the National Academy of Sciences of the United States of America*, is the latest of several studies to add weight to the urgency of repeated calls from U.S. beekeeper and environmental groups for the U.S. Environmental Protection Agency (EPA) to suspend the use of neonicotinoid pesticides, as the European Commission decided this past April.

INSIGHTS


Donna Lisenby
Did Canada Just Have the Largest Coal Slurry Spill in Its History?


Michele Simon
Big Food's Secret Plan to Kill GMO Labeling


Annie Leonard
Reducing Toxic Chemicals in Your Home

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Fracking Victim Sued for Defamation After Proving Drinking Water Flammable

Did Canada Just Have the Largest Coal Slurry Spill in Its History?

Neonicotinoids, a class of insecticides that includes clothianidin and imidicloprid, are taken up by a plant's vascular system and expressed through pollen, nectar and gutation droplets from which bees forage and drink. They are particularly dangerous because—in addition to being acutely toxic in high doses—they also result in serious sublethal effects when insects are exposed to chronic low doses, as they are through pollen and water droplets laced with the chemical, and dust that is released into the air when coated seeds are planted with automated vacuum seed planters. These effects cause significant problems for the health of individual honey bees as well as the overall health of honey bee colonies. Effects include disruptions in bee mobility, navigation, feeding behavior, foraging activity, memory and learning, and overall hive activity.

Up until now, the causal link between insecticide exposure and immune alteration has been unclear. Francesco Pennacchio, Ph.D. of the University of Naples Federico II, and his colleagues identified a gene in insects similar to that found in other animals that is known to regulate the immune response. This gene codes for a leucine-rich repeat protein family (LRR) which has been shown to suppress the activity of a key protein involved in immune signaling, called NF-κB. When the researchers exposed bees to sublethal doses of the neonicotinoid clothianidin, they saw a significant increase in the expression of the gene encoding the LRR protein, and a concomitant suppression of the NF-κB signaling pathway. These effects were not seen when bees were exposed to the organophosphate insecticide chlorpyriphos.

The team infected bees with a common pathogen, deformed wing virus (DWV), and exposed them to clothianidin and another neonicotinoid, imidacloprid, at concentrations similar to those that would be found in the field. The researchers found significantly increased replication of the virus, which was not seen either in untreated bees or those exposed to chlorpyriphos. While the virus is common in bees and usually remains inactive, it is kept in check by the bees' immune system. The data demonstrates that the two neonicotinoids actively promote DWV replication.

"The reported effect on immunity exerted by neonicotinoids will allow additional toxicological tests to be defined to assess if chronic exposure of bees to sub-lethal doses of agrochemicals can adversely affect their immune system and health conditions," says team member Francesco Nazzi, Ph.D. of the University of Udine.

"Moreover, our data indicates the possible occurrence in insects, as in vertebrates, of a neural modulation of the immune response," continued Nazzi. "This sets the stage for future studies in this research area, and poses the question on how neurotoxic substances may affect the immune response."

Since 2006, honey bees nationwide have suffered ongoing and rapid population declines, from hive abandonment and bee die-off in a phenomenon known as colony collapse disorder (CCD). These findings add a significant piece of information to the ongoing and discussion of the role of neonicotinoid pesticides' link to CCD, and, according to researchers, this work has important implications for toxicology and risk assessment studies.

The scientists conclude:

> The results we report clearly indicate the need for longer-term toxicity tests, aiming at assessing how the pathogen progression in honey bees is influenced by insecticide residues and by their cumulative effects, both on adults and larvae. A comprehensive and thorough assessment of insecticide impact on bees will significantly contribute to their conservation and to the development of more sustainable protocols of intensive agriculture.

3 Myths From Pro-Nuclear Film 'Pandora's Promise'

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Huge Election Victories for Colorado's Anti-Fracking Movement

Reducing Toxic Chemicals in Your Home

Yet Another Suspect in CCD/Dwindling?

There have been discussions about neonicotinoids, poor nutrition, Nosema, and mysterious viruses. Now a soil pathologist points a finger at a suspect that's completely under our nose.

The following was written for the Center regarding CCD. Dr. Huber's profile is at the end of this article.

Is glyphosate a contributing cause of bee colony collapse disorder (CCD)?

(Submitted to the Center for Honeybee Research by Dr. Don D. Huber)

Introduction

Bee colony collapse disorder (CCD) is a growing threat to the efficient production of fruits, vegetables and nut crops, in addition to the critical role of bees as pollinators for numerous seed crops (Neumann and Carreck, 2009; Wines, 2013). CCD is characterized as a loss of adult (worker) bees from the hive that leaves the queen and immature bees (brood) inadequately attended even though there is adequate honey and other food present (van Engelsdorp et al, 2006; Wikipedia, 2013). The etiology (*reason)* of CCD is listed as unknown (NFIC, 2013) although neonicotinamid insecticides have been implicated in several studies through disruption of the endocrine hormone system (van Engelsdorp et al, 2006; Tapparo et al, 2012; Wikipedia, 2013) that causes bees to become disoriented and fail to return to the hive (NPIC, 2013).

Acute poisoning and disease leaving dead bees in and around the hive can generally be ruled out, although there is sometimes an increased incidence of *Nosema* and European foul brood (EFB) in stressed colonies that could be contributing factors in some cases (Pettis et al, 2012). Mineral nutritional deficiency is also suspected as a contributing stress factor in CCD (Ahmed, 2012) and malnutrition is the only universal condition found in all cases of CCD even though there is honey and bee-bread generally in the hive. This could be because of toxicity to the Lactobacillus and Bifobacterium species in the honey crop that digest the nectar and render the honey and bee-bread digestible (Ahmed, 2012).

Perhaps a more problematic cause of CCD has been over looked even though it is the most indiscriminately and extensively used chemical in agriculture and the environment. This organic phosphonate chemical that has been overlooked is the estimated 880 million pounds of the popular, broad-spectrum, systemic herbicide glyphosate (also marketed as Roundup®) used for broadcast weed control in general right-of-ways, home gardens, crop production, fallow fields, understory weed control in groves, vineyards, orchards, and parks; and for aquatic weed control in ponds and lakes. It is almost universally used on millions of acres of Roundup Ready® alfalfa, canola, corn, cotton, soybeans and sugar beets. An additional, more recent use has been as a crop desiccant prior to harvest for barley, beans, peas, peanuts, sugar cane, wheat, and for late season weed control in other crops.

These uses have created an extensive exposure level throughout the year with especially high concentrations in plants, air, water and soil during primary bee foraging periods. The exposure, physiological damage, and biological impact of glyphosate are consistent with all of the known conditions related to CCD as shown in Table 1. Of all of the potential individual factors implicated in CCD, glyphosate is the only compound extensively used world-wide where CCD occurs that impacts all of them. That compound, again, is the patented mineral chelator (USPTO, 1964), herbicide, and antibiotic (USPTO, 2000), glyphosate. New studies refer to this compound as the most biologically disruptive chemical in our environment (Samsel and Seneff, 2013). *(E. Note: Samsel and Seneff is worth reading the abstract on the link. You can download the entire PDF, which goes into the modern diseases glyphosate is creating.)*

Table 1. Common characteristics of glyphosate with CCD.

Glyphosate	CCD
Mineral chelator, lowers nutrients in plants condition	Malnutrition (the only universal for all CCD!
Antibiotic to beneficial bacteria *Bifidobacteria* (esp. *Lactobacillus* and *Bifidobacteria* spp.) digestion)	Loss of *Lactobacillus* and (critical beneficial bacteria for
(Low mineral content of plants)	
Neurotoxin	Neurological challenge
Endocrine hormone disruption	Disoriented
Immune suppressant	Suppressed immune system
Stimulates fungal pathogens	*Nosema* increased

Present throughout the foraging period High environmental exposure
Persistent, accumulative
Present in honey, nectar and other plant products

Glyphosate

Glyphosate is an organic phosphonate compound that was first patented as a broad-spectrum, cat-ionic metal chelator by Stauffer Chemical Company in 1964 (USPTO, 1964), as an herbicide by Monsanto Company in 1974 (USPTO, 1974), and as an antibiotic by Monsanto Company in 2000 (USPTO, 2000). All of these uses are based on its ability to 'grab onto' and form a chelate complex that immobilizes mineral nutrients such as Ca, Fe, Co, Cu, Mn, Mg, Ni, Zn, etc. (Glass, 1984). These metal nutrients serve as metal co-factors for various enzyme systems in plants, microorganisms, and animals. Once these metal nutrients are chelated by glyphosate in soil or plants, they become physiologically unavailable as co-factors for many enzymatic and other physiological functions.

The broad-spectrum toxicity of glyphosate to plants initially simplified weed control, especially with selectivity provided by genetically engineered glyphosate-tolerant (Roundup Ready®, RR) plants, so that glyphosate could be applied directly to the RR plants without killing them. This use has led to an estimated annual indiscriminate usage of 880 million pounds of this mineral-immobilizing herbicide and antibiotic in the US. There is nothing in the genetic engineering process, however, that does anything to the glyphosate that is applied to these plants that are foraged by bees.

Glyphosate is systemic in plants: As a phloem mobile chemical, glyphosate from foliar, stem, or root uptake is systemic in plants where it accumulates in flower and reproductive parts, root and shoot tips, and legume nodules (Huber, 2010; Johal and Huber, 2009). Much of the glyphosate will remain in the plant and it can accumulate over years in perennial plants such as alfalfa, vine, fruit, and nut crops and environmental perennial species. It is an active mineral chelator in the treated plant for as many as 8 to 15 days after application before becoming sequestered in flower parts, other meristematic tissues, or soil. As little as 12 gm/acre (1/40th of herbicidal rate and well below the general 12-16 % drift rate) inhibits root uptake and translocation of Fe, Mn, Zn and other nutrients so that plants exposed to glyphosate directly or through drift in air or water have lower nutrient content (Bellaloui et al, 2009, 2011; Bott et al, 2008, 2011; Cakmak et al, 2009; Eker et al, 2006; Huber, 2010, 2012; Zobiole et al 2012).

Minerals in glyphosate-tolerant plants may be impacted even more by glyphosate than those in non-tolerant plants since there is nothing in the genetic engineering that does anything to nullify the glyphosate and its chelating effect on mineral nutrients. Since plant products are the source of essential mineral nutrients, bees may become mineral deficient, malnourished, have a weakened immune system, and be more susceptible to infections and abiotic (*environmental*) stresses.

Direct toxicity of glyphosate: Glyphosate is not acutely toxic to bees, but is chronically toxic to animals, and, like the neonicotinamid insecticides, glyphosate is a neurotoxin and disrupts the endocrine hormone system at very low exposure rates (Antoniou et al, 2012; Gasnier et al, 2009) that are well below levels found in air, water, and, especially, plant tissues (Benbrook, 2012; Huber, 2012).

The 880 million pounds of glyphosate indiscriminately applied throughout the environment leaves glyphosate residues in plants and the environment that can lead to chronic diseases in animals such as autism, botulism, Parkinson's, difficale diarrhea (Clostridium difficile), immune suppression, *Salmonella* and numerous other diseases (Krueger et al, 2012; Shehata et al, 2012).

Disruption of the endocrine hormone system is associated with birth defects. The wide-spread cultivation of glyphosate-tolerant crops (alfalfa, canola, corn, cotton, sugar beets) since 1996 and use as a preharvest desiccant since 2000 have greatly increased the use of glyphosate (Benbrook, 2012; Yamada et al, 2009) and subsequent contamination of air, water, soil, and plant products consistent with the incidence of CCD (NPIC, 2013; Wikipedia, 2013).

Antibiotic activity of glyphosate: Glyphosate is a strong antibiotic and toxic to microorganisms possessing the Shikimate physiological pathway (Johal and Huber, 2009; Kremer and Means, 2009; Krueger et al, 2012; Shehata et al, 2012; USPTO, 2000)). Many of these sensitive microbes include beneficial bacteria such as *Lactobacillus* spp. and *Bifidobacterium* spp. that suppress pathogens such as *Clostridium*, *Salmonella*, *E. coli*, *Nosema*, and American (*Paenibacillus larvae*) and European foul brood (Ahmed, 2012; Clair et al, 2012; Krueger et al, 2012; Shehata et al, 2013). In the absence of these beneficial protective bacteria, the pathogens increase along with the toxins they produce (Krueger et al, 2012; Shehata et al, 2012).

Various fungal pathogens are especially increased in activity and virulence by glyphosate (Johal and Huber, 2009); Kremer et al, 2009; Krueger et al, 2012). All *Apis* species possess a similar *Lactobacillus* and *Bifidobacterium* species microbiota within the honey crop that is critical for collecting and transporting nectar to the hive as well as for the production of honey and bee-bread (Ahmed, 2012). Glyphosate is highly toxic to both of these bacterial species that are necessary for digestion of food and protection from pathogens (Ahmed, 2012; Wikipedia, 2013).

Exposure opportunity: Glyphosate is indiscriminately applied throughout the bee foraging period and is in significant amounts in air, water, and many plant parts frequented by bees. Although not highly volatile, it becomes airborne as drift and on particulate matter with significant levels detected in rain and ground water (USGS, 2012). It is highly water soluble and a common contaminate found in surface water from drift, run-off, or direct application to water for aquatic weed control. It is systemic and persistent in plants with as much as 80% accumulating in meristematic plant tissues such as flowers and buds frequented by bees and is found in honey collected by bees from contaminated flowers. The extensive cultivation of the many glyphosate-tolerant plants has permitted the application of glyphosate before, during, after, and throughout the foraging period of bees to greatly expand the environmental and plant exposure of bees to this organic phosphonate chemical.

This proposal is initiated to determine if glyphosate is a contributing factor in CCD by analyzing exposure of bees to this chemical and its effect on the two predominate bacteria that are essential for bee nutrition and health (Ahmed, 2012). The focus on insecticides and their acute toxicity may have resulted in over-looking the direct and indirect chronic effects of glyphosate as a contributing factor to bee colony collapse disorder.

Proposed Research (Analyses to compare healthy with CCD)

1. Analyze for glyphosate (and AMPA) in pollen, honey (already shown), bee-bread, nectar and bees
2. Determine toxicity of glyphosate (rates) to *Lactobacillus* and *Bifidobacterium species* (already shown for other animals)
3. Endocrine hormone disrupter, neurotoxin, immune suppressant (already shown for other animals)
4. Glyphosate in CCD compared with normal (healthy) hives
5. *Lactobacillus* and *Bifidobacterium* in CCD compared with healthy hives, bees, brood (already shown absent in CCD)

Profile:

- ✓ Dr. Huber is Professor Emeritus of Plant Pathology at Purdue University, West Lafayette, IN. He received B.S. and M.S. degrees from the University of Idaho (1957, 1959), a Ph-D from Michigan State University (1963), and is a graduate of the US Army Command & General Staff College and Industrial College of the Armed Forces. He was at the Department of Botany & Plant Pathology at Purdue University in 1971.

- ✓ His agricultural research the past 50 years has focused on the epidemiology and control of soil-borne plant pathogens with emphasis on microbial ecology, cultural and biological controls, and physiology of host-parasite relationships.

- ✓ He retired in 1995 as Associate Director of the Armed Forces Medical Intelligence Center (Colonel) after 41+ years of active and reserve military service.

- ✓ Dr. Huber is an active scientific reviewer; international research cooperator with projects in Argentina, Australia, Brazil, Chile, China, Costa Rica, Denmark, Germany, Japan, Mexico, and Russia

- ✓ He is internationally recognized for his expertise in the development of nitrification inhibitors to improve the efficiency of N fertilizers, interactions of the form of nitrogen, manganese and other nutrients in disease, herbicide-nutrient-disease interactions, techniques for rapid microbial identification, and cultural control of plant diseases.

- ✓ Dr. Huber teaches courses on anti-crop bioterrorism and serves as a consultant on biological weapons of mass destruction and emerging diseases.

- ✓ To get a more in-depth profile of Dr. Huber, visit: http://www.nvlv.nl/downloads/Dr_Huber_bio.pdf

- ✓ His greatest accomplishment has been his marriage to Paula Huber and their 11 children and 42 grandchildren and 2 great-grandchildren.

The New York Times Reprints

March 29, 2012

2 Studies Point to Common Pesticide as a Culprit in Declining Bee Colonies

By CARL ZIMMER

Scientists have been alarmed and puzzled by declines in bee populations in the United States and other parts of the world. They have suspected that pesticides are playing a part, but to date their experiments have yielded conflicting, ambiguous results.

In Thursday's issue of the journal Science, two teams of researchers published studies suggesting that low levels of a common pesticide can have significant effects on bee colonies. One experiment, conducted by French researchers, indicates that the chemicals fog honeybee brains, making it harder for them to find their way home. The other study, by scientists in Britain, suggests that they keep bumblebees from supplying their hives with enough food to produce new queens.

The authors of both studies contend that their results raise serious questions about the use of the pesticides, known as neonicotinoids.

“I personally would like to see them not being used until more research has been done,” said David Goulson, an author of the bumblebee paper who teaches at the University of Stirling, in Scotland. “If it confirms what we've found, then they certainly shouldn't be used when they're going to be fed on by bees.”

But pesticides are only one of several likely factors that scientists have linked to declining bee populations. There are simply fewer flowers, for example, thanks to land development. Bees are increasingly succumbing to mites, viruses, fungi and other pathogens.

Outside experts were divided about the importance of the two new studies. Some favored the honeybee study over the bumblebee study, while others felt the opposite was true. Environmentalists say that both studies support their view that the insecticides should be banned. And a scientist for Bayer CropScience, the leading maker of neonicotinoids, cast doubt on both studies, for what other scientists said were legitimate reasons.

David Fischer, an ecotoxicologist at Bayer CropScience, said the new experiments had design flaws and conflicting results. In the French study, he said, the honeybees got far too much neonicotinoid. "I think they selected an improper dose level," Dr. Fischer said.

Dr. Goulson's study on bumblebees might warrant a "closer look," Dr. Fischer said, but he argued that the weight of evidence still points to mites and viruses as the most likely candidates for bee declines.

The research does not solve the mystery of the vanishing bees. Although bumblebees have been on the decline in the United States and elsewhere, they have not succumbed to a specific phenomenon known as colony collapse disorder, which affects only honeybees.

Yet the research is coming out at a time when opposition to neonicotinoids is gaining momentum. The insecticides, introduced in the early 1990s, have exploded in popularity; virtually all corn grown in the United States is treated with them. Neonicotinoids are taken up by plants and moved to all their tissues — including the nectar on which bees feed. The concentration of neonicotinoids in nectar is not lethal, but some scientists have wondered if it might still affect bees.

In the honeybee experiment, researchers at the National Institute for Agricultural Research in France fed the bees a dose of neonicotinoid-laced sugar water and then moved them more than half a mile from their hive. The bees carried miniature radio tags that allowed the scientists to keep track of how many returned to the hive.

In familiar territory, the scientists found, the bees exposed to the pesticide were 10 percent less likely than healthy bees to make it home. In unfamiliar places, that figure rose to 31 percent.

The French scientists used a computer model to estimate how the hive would be affected by the loss of these bees. Under different conditions, they concluded that the hive's population might drop by two-thirds or more, depending on how many worker bees were exposed.

"I thought it was very well designed," said May Berenbaum, an entomologist at the University of Illinois at Urbana-Champaign.

But James Cresswell, an ecotoxicologist at the University of Exeter in England, was less impressed, because the scientists had to rely on a computer model to determine changes in the hive. "I don't think the paper is a trump card," he said.

In the British study, Dr. Goulson and his colleagues fed sugar water laced with a neonicotinoid pesticide to 50 bumblebee colonies. The researchers then moved the bee colonies to a farm, alongside 25 colonies that had been fed ordinary sugar water.

At the end of each year, all the bumblebees in a hive die except for a few new queens, which will go on to found new hives. Dr. Goulson and his colleagues found that colonies exposed to neonicotinoids produced 85 percent fewer queens. This reduction would translate into 85 percent fewer hives.

Jeffery Pettis, a bee expert at the United States Department of Agriculture, called Dr. Goulson's study "alarming." He said he suspected that other types of wild bees would be shown to suffer similar effects.

Dr. Pettis is also convinced that neonicotinoids in low doses make bees more vulnerable to disease. He and other researchers have recently published experiments showing that neonicotinoids make honeybees more vulnerable to infections from parasitic fungi.

"Three or four years ago, I was much more cautious about how much pesticides were contributing to the problem," Dr. Pettis said. "Now more and more evidence points to pesticides being a consistent part of the problem."

Roundup Unready

A recent controversial review of scientific research suggests that the active ingredient in Roundup may be more hazardous than previously thought.

Glyphosate, the active ingredient in Roundup and several other brands of herbicide, may be the culprit behind many of the so-called "diseases of civilization" that have plagued humanity since the last third of the 20th century and are escalating at alarming rates today. These diseases and conditions include gastrointestinal disorders, obesity, diabetes, heart disease, depression, autism, infertility, cancer, Alzheimer's disease, Parkinson's disease, birth defects, and more.

That's the conclusion of two scientists who reviewed 286 studies of the biological effects of glyphosate and published their findings in the peer-reviewed journal *Entropy* in April 2013. These findings are a bombshell that, if confirmed by further studies, could lead to a worldwide ban on glyphosate.

In their search of the literature, environmental scientist Anthony Samsel and Stephanie Seneff, senior research scientist at Massachusetts Institute of Technology's Computer Science and Artificial Intelligence Laboratory, found that glyphosate suppresses and inhibits cytochrome P45, a class of human enzyme known in scientific shorthand as CYP.

Worldwide, nearly 1 million metric tons of glyphosate is used annually, mostly on food crops, according to Global Industry Analysts.

ALAN SPENCER/ALAMY

Inhibiting enzymes is exactly how glyphosate works as an herbicide. Enzymes are catalysts for all sorts of functions in plants, and when they are suppressed, the plants die for lack of the ability to function properly. Something of the same effect may be at work in humans who ingest glyphosate on their food.

"Glyphosate's inhibition of CYP enzymes is an overlooked component of its toxicity to mammals," Samsel and Seneff write. "CYP enzymes play crucial roles in biology, one of which is to detoxify any foreign substances not normally found in living creatures, such as pesticides, industrial chemicals, pollutants, and drugs. Thus, glyphosate enhances the damaging effects of other food-borne chemical residues and environmental toxins. The negative impact on the body is insidious, and manifests slowly over time as inflammation damages cellular systems within the body."

The authors describe how glyphosate harms three crucial bodily functions. First, it interferes with CYP enzymes. Second, it disrupts the ability of intestinal microbes to construct important amino acids that build and repair the body's cellular tissues. Third, it impairs the movement of sulfate compounds in the blood. These compounds are especially important in the growth of infants, young children, and developing fetuses. Glyphosate's enzyme inhibition acts synergistically with the other two damaging effects; that is, it produces a more serious health effect than the sum of the individual effects.

Samsel and Seneff conclude with a plea for more independent research. "Glyphosate is likely to be pervasive in our food supply," they write, "and contrary to being essentially non-toxic, it may in fact be the most biologically disruptive chemical in our environment."

What the authors have done in this review of the scientific literature on glyphosate is to connect the dots, with each dot being one of the 286 studies. *Entropy*, which published the article, is an online open-access journal that is willing to publish novel hypotheses regarding biochemical and biophysical phenomena. The papers in the journal are subjected to review by experts who are not beholden to industry influence. Publishing fees are paid by the authors or their institutions.

Samsel is a long-time environmental scientist, now retired, who operates an organic farm on 5 acres in New Hampshire. Seneff became interested in glyphosate through her research on autism. Their review was funded by Quanta Computers, a notebook computer and cloud computing company based in Taiwan. "We did not do any new research other than predict the likely consequences of glyphosate, given the evidence available in the papers we reviewed," Seneff says.

Of course, the study has raised the hackles of those who think glyphosate is great stuff. Skeptics have lined up to discredit the paper and its authors. But Samsel and Seneff have simply combed the literature to see what science has found out about glyphosate, and they've come to the conclusion that the chemical has extremely deleterious effects on human health. Let those who argue otherwise point out the flaws in the 286 studies the authors have pored through, rather than attacking the authors for doing good research. —*Jeff Cox*

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Portuguese Medical Association President Calls for Global Ban on Glyphosate

Posted on Feb 9 2016 - 2:58pm **by** Sustainable Pulse

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The President of the Portuguese Medical Association, José Manuel Silva, has called for a Global ban on the World's most used herbicide, Glyphosate, over the many health concerns surrounding the chemical.

Editorial by José Manuel Silva, President, Portuguese Medical Association. Published first in Portuguese in the July/August 2015 issue of the Portuguese Medical Association Magazine.

The New Statutory Rights of the Portuguese Medical Association and Glyphosate

It may seem odd, but there is a connection! The Portuguese Parliament approved the new statutes of the Portuguese Medical Association, which will allow for a significant improvement in its management, organization and response time. After complex and laborious negotiations, a process that many feared finally reached its end in a reasonably satisfactory fashion, respecting and reinforcing the abilities and interventional skills of the Association. In the future I shall comment on the new statutes that are now being sent to the nation's President for almost certain enactment. There are many substantial changes.

One I intend to underline here is the creation of the Association's National Consultative Council on Ecology and Health Promotion. Obviously many people don't feel ecology is the main issue of the moment, but it is truly the future of life on

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Earth that is at stake. This is not a drill… Even Pope Francis has been emphasizing ecological issues and the threat of global warming.

Considering records show that the Earth lost 30% of its wildlife in the last 100 years and another 50% could be extinguished before the end of the century, that 2015 may well be the hottest year on record, and that current levels of consumption require 1.5 planets (4 planets for a US lifestyle and 2.5 for the UK's), the Portuguese Medical Association could not continue to ignore the many serious implications environmental issues have on Health and Life. These are new dimensions for doctors to intervene in society and frame the Association's approach to improved protection of patients, doctors and health itself.

In fact, the planet's sustainability and environment related diseases are the major vital and ethical challenges for humanity and medicine. Many examples could be named. One of those is glyphosate, better known as Roundup, its commercial name. This is the most used herbicide in Portuguese agriculture and urban areas for weed control.

In the last decade glyphosate use has increased about 50%, with 1400 tons applied in 2010 alone. In total, more than 130 million tons a year are used around the world. Because of this glyphosate is routinely detected in food, air, rainwater and rivers, urine, blood and even breast milk. Its presence is so overwhelming that legal limits had to be stretched in order for it to continue being used, with serious potential and cumulative risks to human health. In the European Union, in 1999, the maximum acceptable level for glyphosate in soy was increased 200% (from 0,1 to 20mg/kg) and in 2013, the US government also increased the tolerance level on dozens of crops. Other countries, and even the Codex Alimentarius, have been going the same route. We must not forget that the genetically modified foods and seeds of plants designed to tolerate glyphosate can carry higher concentrations of this toxin, which is used to kill 'weeds' more freely in these cases.

Recent articles show the epidemiological connection and the biological plausibility of glyphosate being a risk factor for the increase in celiac disease, infertility, congenital malformations, kidney disease, autism and other pathologies (*Interdiscip Toxicol*, 2013; 6 (4): 159-84 // *Int J Environ Res Public Health*, 2014; 11: 2125-147 // *Surg Neurol Int*, 2015; 6: 45). Mortality in acute intoxication varies between 3.2 and 29.3%, mostly by pulmonary and / or kidney disease. The various pathological mechanisms for glyphosate are well-known and include changes in the intestinal micro-biome, disruption of cytochrome P450, vitamin deficiencies, metal chelation, molybdenum and selenium deficiencies, etc.

An additional concern is the fact that the International Agency for Research on Cancer (IARC) announced, in March 2015, that glyphosate had been classified as a "probable carcinogen". The IARC is the world's leading authority on cancer and this decision was unanimous among the 17 experts of the panel headed by Dr. Aaron Blair, a geneticist, who for 30 years led the occupational cancer unit at the US National Cancer Institute.

The IARC assessed firsthand all the relevant scientific research published to date, namely in epidemiological terms. The reason glyphosate wasn't classified as fully carcinogenic to humans, was because of the limited epidemiological evidence, whose studies are particularly complex. Three of these studies show a connection between glyphosate exposure and non-Hodgkin lymphoma (NHL), whose incidence has increased significantly in the last 30 years, while a fourth study points to multiple myeloma but finds no connection to NHL.

Although, according to the IARC, the evidence in humans is not clearly incriminating (as has happened, in an initial phase, with so many toxins), it is extremely worrying. It is not easy to show this connection because there is a hiatus – sometimes dozens of years long – between carcinogen exposure and appearance of the "corresponding" cancer.

As if all this wasn't enough, two additional issues suggest the IARC is erring on the conservative side. The first is that evaluations have focused on the active ingredient – glyphosate itself – even though the commercial formulation contains other chemical compounds. Consistent research shows that a significant share of the pesticides' total toxicity may be attributed to these adjuvants (*BioMed Research International. Vol 2014, Article ID 179691*). Despite its benign reputation, Roundup is among the most toxic herbicides used in the European Union.

Furthermore, human beings are exposed simultaneously to chemical compounds of multiple origins which may interact synergistically. Some examples are well-known in toxicology: carbon tetrachloride and ethanol, together, have a far more devastating effect on the liver than the sum of their individual impacts. But even if the effects resulted from a summation only, with no synergies, none of that is taken into account when evaluating risks, approving the compounds and establishing classifications or limits. It is also noteworthy that those living in the western world carry in their bodies hundreds of synthetic contaminants that didn't even exist 200 years ago.

Taken together, this data suggests that a careful reflection on glyphosate's future, and globally on the management of food chemical risks, is in order. The worldwide acknowledged precautionary principle says that, in the face of clear evidence of harm, action to protect human health and the environment should not wait for final scientific evidence. For glyphosate the conclusion is clear: this herbicide should be banned worldwide.

Who should take action in Portugal? Without a doubt, the Government and the Directorate-General for Health must take the lead. Economic interests cannot, and must not, suppress the moral imperative of citizen health protection. The sluggishness of legal procedures does not excuse inertia either. European law allows temporary safeguard clauses to be quickly invoked until science comes up with final answers.

Cancers of unknown origin abound, and the highly chemical and industrialized society we live in is certainly partly responsible. In the future, it should be possible to improve this state of affairs. However, for those cancers which can already be avoided in the present, governmental inaction is unacceptable.

As for doctors, they cannot continue to alienate themselves from these environmental issues without failing health prevention – the main focus of their mission – and many disease diagnoses. Glyphosate is just one example among many…

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Sustainable Pulse provides the general public with the latest global news on GMOs, Sustainable Food and Sustainable Agriculture from our network of worldwide sources.

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"If the kind of detrimental effects seen in animals fed GM food were observed in a clinical setting, the use of the product would have been halted and further research instigated to determine the cause and find possible solutions. However, what we find repeatedly in the case of GM food is that both governments and industry plough on ahead with the development, endorsement, and marketing [of] GM foods despite the warnings of potential ill health from animal feeding studies, as if nothing has happened. This is to the point where governments and industry even seem to ignore the results of their own research! There is clearly a need more than ever before for independent research into the potential ill effects of GM food including most importantly extensive animal and human feeding trials."[1]

—Michael Antoniou, molecular geneticist,
King's College London

"The products of genetic engineering today are still at the level of a dinosaur technology. We use genes, which are foreign to a species, not knowing where they are inserted or what else will change in the whole chain from gene to protein."[1]

—Cesare Gessler, The ETH Swiss Federal
Institute of Technology

"The default prediction for the impacts of expression of a new gene (and its products) within a transgenic organism would . . . be that this expression will be accompanied by a range of collateral changes in expression of other genes, changes in the pattern of proteins produced and/or changes in metabolic activities."[2]

—The Royal Society of Canada

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Why genetically engineered food is dangerous: New report by genetic engineers

Earth Open Source press release 17 June 2012

Aren't critics of genetically engineered food anti-science? Isn't the debate over GMOs (genetically modified organisms) a spat between emotional but ignorant activists on one hand and rational GM-supporting scientists on the other?

A new report released today, "GMO Myths and Truths",[1] challenges these claims. The report presents a large body of peer-reviewed scientific and other authoritative evidence of the hazards to health and the environment posed by genetically engineered crops and organisms (GMOs).

Unusually, the initiative for the report came not from campaigners but from two genetic engineers who believe there are good scientific reasons to be wary of GM foods and crops.


Dr Michael Antoniou

One of the report's authors, Dr Michael Antoniou of King's College London School of Medicine in the UK, uses genetic engineering for medical applications but warns against its use in developing crops for human food and animal feed.

Dr Antoniou said: "GM crops are promoted on the basis of ambitious claims - that they are safe to eat, environmentally beneficial, increase yields, reduce reliance on pesticides, and can help solve world hunger.

"I felt what was needed was a collation of the evidence that addresses the technology from a scientific point of view.

"Research studies show that genetically modified crops have harmful effects on laboratory animals in feeding trials and on the environment during cultivation. They have increased the use of pesticides and have failed to increase yields. Our report concludes that there are safer and more effective alternatives to meeting the world's food needs."


Dr John Fagan

Another author of the report, Dr John Fagan, is a former genetic engineer who in 1994 returned to the National Institutes of Health $614,000 in grant money due to concerns about the safety and ethics of the technology. He subsequently founded a GMO testing company.

Dr Fagan said: "Crop genetic engineering as practiced today is a crude, imprecise, and outmoded technology. It can create unexpected toxins or allergens in foods and affect their nutritional value. Recent advances point to better ways of using our knowledge of genomics to improve food crops, that do not involve GM.

"Over 75% of all GM crops are engineered to tolerate being sprayed with herbicide. This has led to the spread of herbicide-resistant superweeds and has resulted in massively increased exposure of farmers and communities to these toxic chemicals. Epidemiological studies suggest a link between herbicide use and birth defects and cancer.

Claire Robinson

"These findings fundamentally challenge the utility and safety of GM crops, but the biotech industry uses its influence to block research by independent scientists and uses its powerful PR machine to discredit independent scientists whose findings challenge this approach."

The third author of the report, Claire Robinson, research director of Earth Open Source, said, "The GM industry is trying to change our food supply in

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Less polite German version of proverb: "Science advances when the old idiots die."

"Old theories never die, they just fade away with their proponents." Old proverb.

far-reaching and potentially dangerous ways. We all need to inform ourselves about what is going on and ensure that we - not biotechnology companies - keep control of our food system and crop seeds.

"We hope our report will contribute to a broader understanding of GM crops and the sustainable alternatives that are already working successfully for farmers and communities."

Notes

The report, "GMO Myths and Truths, An evidence-based examination of the claims made for the safety and efficacy of genetically modified crops", by Michael Antoniou, PhD, Claire Robinson, and John Fagan, PhD is published by Earth Open Source (June 2012). The report is 123 pages long and contains over 600 citations, many of them from the peer-reviewed scientific literature and the rest from reports by scientists, physicians, government bodies, industry, and the media. The report is available here: http://earthopensource.org/index.php/reports/58

A shorter summary version will be released in the coming weeks.

Key points from the report

1. Genetic engineering as used in crop development is not precise or predictable and has not been shown to be safe. The technique can result in the unexpected production of toxins or allergens in food that are unlikely to be spotted in current regulatory checks.
2. GM crops, including some that are already in our food and animal feed supply, have shown clear signs of toxicity in animal feeding trials - notably disturbances in liver and kidney function and immune responses.
3. GM proponents have dismissed these statistically significant findings as "not biologically relevant/significant", based on scientifically indefensible arguments.
4. Certain EU-commissioned animal feeding trials with GM foods and crops are often claimed by GM proponents to show they are safe. In fact, examination of these studies shows significant differences between the GM-fed and control animals that give cause for concern.
5. GM foods have not been properly tested in humans, but the few studies that have been carried out in humans give cause for concern.
6. The US FDA does not require mandatory safety testing of GM crops, and does not even assess the safety of GM crops but only "deregulates" them, based on assurances from biotech companies that they are "substantially equivalent" to their non-GM counterparts. This is like claiming that a cow with BSE is substantially equivalent to a cow that does not have BSE and is thus safe to eat! Claims of substantial equivalence cannot be justified on scientific grounds.
7. The regulatory regime for GM foods is weakest in the US, where GM foods do not even have to be assessed for safety or labelled in the marketplace, but in most regions of the world regulations are inadequate to protect people's health from the potential adverse effects of GM foods.
8. In the EU, where the regulatory system is often claimed to be strict, minimal pre-market testing is required for a GMO and the tests are commissioned by the same companies that stand to profit from the GMO if it is approved - a clear conflict of interest.
9. No long-term toxicological testing of GMOs on animals or testing on humans is required by any regulatory agency in the world.
10. Biotech companies have used patent claims and intellectual property protection laws to restrict access of independent researchers to GM crops for research purposes. As a result, limited research has been conducted on GM foods and crops by scientists who are independent of the GM industry. Scientists whose work has raised concerns about the safety of GMOs have been attacked and discredited in orchestrated campaigns by GM crop promoters.
11. Most GM crops (over 75%) are engineered to tolerate applications of herbicides. Where such GM crops have been adopted, they have led to massive increases in herbicide use.
12. Roundup, the herbicide that over 50% of all GM crops are engineered to tolerate, is not safe or benign as has been claimed but has been found to cause malformations (birth defects), reproductive problems, DNA damage, and cancer in test animals. Human epidemiological studies have found an association between Roundup exposure and miscarriage, birth defects, neurological development problems, DNA damage, and certain types of cancer.
13. A public health crisis has erupted in GM soy-producing regions of South America, where people exposed

to spraying with Roundup and other agrochemicals sprayed on the crop report escalating rates of birth defects and cancer.

14. A large number of studies indicate that Roundup is associated with increased crop diseases, especially infection with Fusarium, a fungus that causes wilt disease in soy and can have toxic effects on humans and livestock.
15. Bt insecticidal GM crops do not sustainably reduce pesticide use but change the way in which pesticides are used: from sprayed on, to built in.
16. Bt technology is proving unsustainable as pests evolve resistance to the toxin and secondary pest infestations are becoming common.
17. GM proponents claim that the Bt toxin engineered into GM plants is safe because the natural form of Bt, long used as a spray by conventional and organic farmers, has a history of safe use. But the GM forms of Bt toxins are different from the natural forms and could have different toxic and allergenic effects.
18. GM Bt toxin is not limited in its toxicity to insect pests. GM Bt crops have been found to have toxic effects on laboratory animals in feeding trials.
19. GM Bt crops have been found to have toxic effects on non-target organisms in the environment.
20. Bt toxin is not fully broken down in digestion and has been found circulating in the blood of pregnant women in Canada and in the blood supply to their foetuses.
21. The no-till method of farming promoted with GM herbicide-tolerant crops, which avoids ploughing and uses herbicides to control weeds, is not more climate-friendly than ploughing. No-till fields do not store more carbon in the soil than ploughed fields when deeper levels of soil are measured.
22. No-till increases the negative environmental impacts of soy cultivation, because of the herbicides used.
23. Golden Rice, a beta-carotene-enriched rice, is promoted as a GM crop that could help malnourished people overcome vitamin A deficiency. But Golden Rice has not been tested for toxicological safety, has been plagued by basic development problems, and, after more than 12 years and millions of dollars of research funding, is still not ready for the market. Meanwhile, inexpensive and effective solutions to vitamin A deficiency are available but under-used due to lack of funding.
24. GM crops are often promoted as a "vital tool in the toolbox" to feed the world's growing population, but many experts question the contribution they could make, as they do not offer higher yields or cope better with drought than non-GM crops. Most GM crops are engineered to tolerate herbicides or to contain a pesticide - traits that are irrelevant to feeding the hungry.
25. High adoption of GM crops among farmers is not a sign that the GM crop is superior to non-GM varieties, as once GM companies gain control of the seed market, they withdraw non-GM seed varieties from the market. The notion of "farmer choice" does not apply in this situation.
26. GM contamination of non-GM and organic crops has resulted in massive financial losses by the food and feed industry, involving product recalls, lawsuits, and lost markets.
27. When many people read about high-yielding, pest- and disease-resistant, drought-tolerant, and nutritionally improved super-crops, they think of GM. In fact, these are all products of conventional breeding, which continues to outstrip GM in producing such crops. The report contains a long list of these conventional crop breeding successes.
28. Certain "supercrops" have been claimed to be GM successes when in fact they are products of conventional breeding, in some cases assisted by the non-GM biotechnology of marker assisted selection.
29. Conventional plant breeding, with the help of non-GM biotechnologies such as marker assisted selection, is a safer and more powerful method than GM to produce new crop varieties required to meet current and future needs of food production, especially in the face of rapid climate change.
30. Conventionally bred, locally adapted crops, used in combination with agroecological farming practices, offer a proven, sustainable approach to ensuring global food security.

About the authors

Michael Antoniou, PhD is reader in molecular genetics and head, Gene Expression and Therapy Group, King's College London School of Medicine, London, UK. He has 28 years' experience in the use of genetic engineering technology investigating gene organisation and control, with over 40 peer reviewed publications of original work, and holds inventor status on a number of gene expression biotechnology patents. Dr Antoniou has a large network of collaborators in industry and academia who are making use of his discoveries in gene control mechanisms for the production of research, diagnostic and therapeutic products and human somatic gene therapies for inherited and acquired genetic disorders.

John Fagan, PhD is a leading authority on sustainability in the food system, biosafety, and GMO testing. He is founder and chief scientific officer of a GMO testing and certification company. He is a director of Earth Open Source. Earlier, he conducted cancer research at the US National Institutes of Health (NIH) and in

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10/21/13

Statement: No scientific consensus on GMO safety

As scientists, physicians, academics, and experts from disciplines relevant to the scientific, legal, social and safety assessment aspects of genetically modified organisms (GMOs),[1] we strongly reject claims by GM seed developers and some scientists, commentators, and journalists that there is a "scientific consensus" on GMO safety[2] [3] [4] and that the debate on this topic is "over".[5]

We feel compelled to issue this statement because the claimed consensus on GMO safety does not exist. The claim that it does exist is misleading and misrepresents the currently available scientific evidence and the broad diversity of opinion among scientists on this issue. Moreover, the claim encourages a climate of complacency that could lead to a lack of regulatory and scientific rigour and appropriate caution, potentially endangering the health of humans, animals, and the environment.

Science and society do not proceed on the basis of a constructed consensus, as current knowledge is always open to well-founded challenge and disagreement. We endorse the need for further independent scientific inquiry and informed public discussion on GM product safety and urge GM proponents to do the same.

Some of our objections to the claim of scientific consensus are listed below.

1. There is no consensus on GM food safety

Regarding the safety of GM crops and foods for human and animal health, a comprehensive review of animal feeding studies of GM crops found "An equilibrium in the number [of] research groups suggesting, on the basis of their studies, that a number of varieties of GM products (mainly maize and soybeans) are as safe and nutritious as the respective conventional non-GM plant, and those raising still serious concerns". The review also found that most studies concluding that GM foods were as safe and nutritious as those obtained by conventional breeding were "performed by biotechnology companies or associates, which are also responsible [for] commercializing these GM plants".[6]

A separate review of animal feeding studies that is often cited as showing that GM foods are safe included studies that found significant differences in the GM-fed animals. While the review authors dismissed these findings as not biologically significant,[7] the interpretation of these differences is the subject of continuing scientific debate[8] [9] [10] [11] and no consensus exists on the topic.

Rigorous studies investigating the safety of GM crops and foods would normally involve animal feeding studies in which one group of animals is fed GM food and another group is fed an equivalent non-GM diet. Independent studies of this type are rare, but when such studies have been performed,

View the signatories as of 20 January 2015

"No sciencific consensus" statement published in Environmental Sciences Europe

Sign the statement "No consensus on GMO safety"

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Find here ENSSER's mission statement, statute and membership application form widespread exposure of human and animal populations to GM crops.

A statement by the board of directors of the American Association for the Advancement of Science (AAAS) affirming the safety of GM crops and opposing labelling[25] cannot be assumed to represent the view of AAAS members as a whole and was challenged in an open letter by a group of 21 scientists, including many long-standing members of the AAAS.[26] This episode underlined the lack of consensus among scientists about GMO safety.

4. EU research project does not provide reliable evidence of GM food safety

An EU research project[27] has been cited internationally as providing evidence for GM crop and food safety. However, the report based on this project, "A Decade of EU-Funded GMO Research", presents no data that could provide such evidence, from long-term feeding studies in animals.

Indeed, the project was not designed to test the safety of any single GM food, but to focus on "the development of safety assessment approaches".[28] Only five published animal feeding studies are referenced in the SAFOTEST section of the report, which is dedicated to GM food safety.[29] None of these studies tested a commercialised GM food; none tested the GM food for long-term effects beyond the subchronic period of 90 days; all found differences in the GM-fed animals, which in some cases were statistically significant; and none concluded on the safety of the GM food tested, let alone on the safety of GM foods in general. Therefore the EU research project provides no evidence for sweeping claims about the safety of any single GM food or of GM crops in general.

5. List of several hundred studies does not show GM food safety

A frequently cited claim published on an Internet website that several hundred studies "document the general safety and nutritional wholesomeness of GM foods and feeds"[30] is misleading. Examination of the studies listed reveals that many do not provide evidence of GM food safety and, in fact, some provide evidence of a lack of safety. For example:

- Many of the studies are not toxicological animal feeding studies of the type that can provide useful information about health effects of GM food consumption. The list includes animal production studies that examine parameters of interest to the food and agriculture industry, such as milk yield and weight gain;[31] [32] studies on environmental effects of GM crops; and analytical studies of the composition or genetic makeup of the crop.
- Among the animal feeding studies and reviews of such studies in the list, a substantial number found toxic effects and signs of toxicity in GM-fed animals compared with controls.[33] [34] [35] [36] [37] [38] Concerns raised by these studies have not been satisfactorily addressed and the claim that the body of research shows a consensus over the safety of GM crops and foods is false and irresponsible.
- Many of the studies were conducted over short periods compared with the animal's total lifespan and cannot detect long-term health effects. [39] [40]

We conclude that these studies, taken as a whole, are misrepresented on the Internet website as they do not "document the general safety and nutritional wholesomeness of GM foods and feeds". Rather, some of the studies give some have revealed toxic effects or signs of toxicity in the GM-fed animals.[12] [13] [14] [15] [16] [17] The concerns raised by these studies have not been followed up by targeted research that could confirm or refute the initial findings.

The lack of scientific consensus on the safety of GM foods and crops is underlined by the recent research calls of the European Union and the French government to investigate the long-term health impacts of GM food consumption in the light of uncertainties raised by animal feeding studies.[18] [19] These official calls imply recognition of the inadequacy of the relevant existing scientific research protocols. They call into question the claim that existing research can be deemed conclusive and the scientific debate on biosafety closed.

2. There are no epidemiological studies investigating potential effects of GM food consumption on human health

It is often claimed that "trillions of GM meals" have been eaten in the US with no ill effects. However, no epidemiological studies in human populations have been carried out to establish whether there are any health effects associated with GM food consumption. As GM foods are not labelled in North America, a major producer and consumer of GM crops, it is scientifically impossible to trace, let alone study, patterns of consumption and their impacts. Therefore, claims that GM foods are safe for human health based on the experience of North American populations have no scientific basis.

3. Claims that scientific and governmental bodies endorse GMO safety are exaggerated or inaccurate

Claims that there is a consensus among scientific and governmental bodies that GM foods are safe, or that they are no more risky than non-GM foods,[20] [21] are false.

For instance, an expert panel of the Royal Society of Canada issued a report that was highly critical of the regulatory system for GM foods and crops in that country. The report declared that it is "scientifically unjustifiable" to presume that GM foods are safe without rigorous scientific testing and that the "default prediction" for every GM food should be that the introduction of a new gene will cause "unanticipated changes" in the expression of other genes, the pattern of proteins produced, and/or metabolic activities. Possible outcomes of these changes identified in the report included the presence of new or unexpected allergens.[22]

A report by the British Medical Association concluded that with regard to the long-term effects of GM foods on human health and the environment, "many unanswered questions remain" and that "safety concerns cannot, as yet, be dismissed completely on the basis of information currently available". The report called for more research, especially on potential impacts on human health and the environment.[23]

Moreover, the positions taken by other organizations have frequently been highly qualified, acknowledging data gaps and potential risks, as well as potential benefits, of GM technology. For example, a statement by the American Medical Association's Council on Science and Public Health acknowledged "a small potential for adverse events … due mainly to horizontal gene transfer, allergenicity, and toxicity" and recommended that the current voluntary notification procedure practised in the US prior to market release of GM crops be made mandatory.[24] It should be noted that even a "small potential for adverse events" may turn out to be significant, given the serious cause for concern and should be followed up by more detailed investigations over an extended period of time.

6. There is no consensus on the environmental risks of GM crops

Environmental risks posed by GM crops include the effects of Bt insecticidal crops on non-target organisms and effects of the herbicides used in tandem with herbicide-tolerant GM crops.

As with GM food safety, no scientific consensus exists regarding the environmental risks of GM crops. A review of environmental risk assessment approaches for GM crops identified shortcomings in the procedures used and found "no consensus" globally on the methodologies that should be applied, let alone on standardized testing procedures.[41]

Some reviews of the published data on Bt crops have found that they can have adverse effects on non-target and beneficial organisms[42] [43] [44] [45] – effects that are widely neglected in regulatory assessments and by some scientific commentators. Resistance to Bt toxins has emerged in target pests,[46] and problems with secondary (non-target) pests have been noted, for example, in Bt cotton in China.[47] [48]

Herbicide-tolerant GM crops have proved equally controversial. Some reviews and individual studies have associated them with increased herbicide use,[49] [50] the rapid spread of herbicide-resistant weeds,[51] and adverse health effects in human and animal populations exposed to Roundup, the herbicide used on the majority of GM crops.[52] [53] [54]

As with GM food safety, disagreement among scientists on the environmental risks of GM crops may be correlated with funding sources. A peer-reviewed survey of the views of 62 life scientists on the environmental risks of GM crops found that funding and disciplinary training had a significant effect on attitudes. Scientists with industry funding and/or those trained in molecular biology were very likely to have a positive attitude to GM crops and to hold that they do not represent any unique risks, while publicly-funded scientists working independently of GM crop developer companies and/or those trained in ecology were more likely to hold a "moderately negative" attitude to GM crop safety and to emphasize the uncertainty and ignorance involved. The review authors concluded, "The strong effects of training and funding might justify certain institutional changes concerning how we organize science and how we make public decisions when new technologies are to be evaluated."[55]

7. International agreements show widespread recognition of risks posed by GM foods and crops

The Cartagena Protocol on Biosafety was negotiated over many years and implemented in 2003. The Cartagena Protocol is an international agreement ratified by 166 governments worldwide that seeks to protect biological diversity from the risks posed by GM technology. It embodies the Precautionary Principle in that it allows signatory states to take precautionary measures to protect themselves against threats of damage from GM crops and foods, even in case of a lack of scientific certainty.[56]

Another international body, the UN's Codex Alimentarius, worked with scientific experts for seven years to develop international guidelines for the assessment of GM foods and crops, because of concerns about the risks they pose. These guidelines were adopted by the Codex Alimentarius Commission, of which over 160 nations are members, including major GM crop producers such as the United States.[57]

The Cartagena Protocol and Codex share a precautionary approach to GM crops and foods, in that they agree that genetic engineering differs from conventional breeding and that safety assessments should be required before GM organisms are used in food or released into the environment.

These agreements would never have been negotiated, and the implementation processes elaborating how such safety assessments should be conducted would not currently be happening, without widespread international recognition of the risks posed by GM crops and foods and the unresolved state of existing scientific understanding.

Concerns about risks are well-founded, as has been demonstrated by studies on some GM crops and foods that have shown adverse effects on animal health and non-target organisms, indicated above. Many of these studies have, in fact, fed into the negotiation and/or implementation processes of the Cartagena Protocol and Codex. We support the application of the Precautionary Principle with regard to the release and transboundary movement of GM crops and foods.

Conclusion

In the scope of this document, we can only highlight a few examples to illustrate that the totality of scientific research outcomes in the field of GM crop safety is nuanced, complex, often contradictory or inconclusive, confounded by researchers' choices, assumptions, and funding sources, and in general, has raised more questions than it has currently answered.

Whether to continue and expand the introduction of GM crops and foods into the human food and animal feed supply, and whether the identified risks are acceptable or not, are decisions that involve socioeconomic considerations beyond the scope of a narrow scientific debate and the currently unresolved biosafety research agendas. These decisions must therefore involve the broader society. They should, however, be supported by strong scientific evidence on the long-term safety of GM crops and foods for human and animal health and the environment, obtained in a manner that is honest, ethical, rigorous, independent, transparent, and sufficiently diversified to compensate for bias.

Decisions on the future of our food and agriculture should not be based on misleading and misrepresentative claims that a "scientific consensus" exists on GMO safety.

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[1] In the US, the term "genetically engineered" is often used in place of "genetically modified". We have used "genetically modified" because this is the terminology consistently used by many authorities internationally, including the Food and Agriculture Organization of the United Nations; the World Health Organization; Codex Alimentarius; European and Indian legislation; peer-reviewed studies by industry and independent scientists; and the international media. It is also consistent with the Cartagena Protocol's term "living modified organism".

[2] Frewin, G. (2013). The new "is GM food safe?" meme. Axis Mundi, 18 July. http://www.axismundionline.com/blog/the-new-is-gm-food-safe-meme/; Wikipedia (2013). Genetically modified food controversies. http://en.wikipedia.org/wiki/Genetically_modified_food_controversies

Dr. Michael Antoniou: Roundup Causes Massive Kidney and Liver Damage at Low Doses

A new ground-breaking peer-reviewed study has been published in Environmental Health Journal that shows the levels of glyphosate-based herbicides which the general public are commonly exposed to in drinking water, altered the gene function of over 4000 genes in the livers and kidneys of rats.

Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure

Full Paper: http://www.ehjournal.net/content/14/1/70

Authors: **Robin Mesnage, Matthew Arno, Manuela Costanzo, Manuela Malatesta, Gilles-Eric Séralini** and **Michael N. Antoniou**

Abstract:

Background

Glyphosate-based herbicides (GBH) are the major pesticides used worldwide. Converging evidence suggests that GBH, such as Roundup, pose a particular health risk to liver and kidneys although low environmentally relevant doses have not been examined. To address this issue, a 2-year study in rats administering 0.1 ppb Roundup (50 ng/L glyphosate equivalent) via drinking water (giving a daily intake of 4 ng/kg bw/day of glyphosate) was conducted. A marked increased incidence of anatomorphological and blood/urine biochemical changes was indicative of liver and kidney structure and functional pathology. In order to confirm these findings we have conducted a transcriptome microarray analysis of the liver and kidneys from these same animals.

Results

The expression of 4224 and 4447 transcript clusters (a group of probes corresponding to a known or putative gene) were found to be altered respectively in liver and kidney ($p < 0.01$, $q < 0.08$). Changes in gene expression varied from −3.5 to 3.7 fold in liver and from

–4.3 to 5.3 in kidneys. Among the 1319 transcript clusters whose expression was altered in both tissues, ontological enrichment in 3 functional categories among 868 genes were found. First, genes involved in mRNA splicing and small nucleolar RNA were mostly upregulated, suggesting disruption of normal spliceosome activity. Electron microscopic analysis of hepatocytes confirmed nucleolar structural disruption. Second, genes controlling chromatin structure (especially histone-lysine N-methyltransferases) were mostly upregulated. Third, genes related to respiratory chain complex I and the tricarboxylic acid cycle were mostly downregulated. Pathway analysis suggests a modulation of the mTOR and phosphatidylinositol signalling pathways. Gene disturbances associated with the chronic administration of ultra-low dose Roundup reflect a liver and kidney lipotoxic condition and increased cellular growth that may be linked with regeneration in response to toxic effects causing damage to tissues. Observed alterations in gene expression were consistent with fibrosis, necrosis, phospholipidosis, mitochondrial membrane dysfunction and ischemia, which correlate with and thus confirm observations of pathology made at an anatomical, histological and biochemical level.

Conclusion

Our results suggest that chronic exposure to a GBH in an established laboratory animal toxicity model system at an ultra-low, environmental dose can result in liver and kidney damage with potential significant health implications for animal and human populations.

Roundup: Birth Defects Caused By World's Top-Selling Weedkiller, Scientists Say

06/24/2011 09:04 am ET | **Updated** Aug 24, 2011

- Lucia Graves

WASHINGTON -- The chemical at the heart of the planet's most widely used herbicide -- Roundup weedkiller, used in farms and gardens across the U.S. -- is coming under more intense scrutiny following the release of a new report calling for a heightened regulatory response around its use.

Critics have argued for decades that glyphosate, the active ingredient in Roundup and other herbicides used around the globe, poses a serious threat to public health. Industry regulators, however, appear to have consistently overlooked their concerns.

A comprehensive review of existing data released this month by Earth Open Source, an organization that uses open-source collaboration to advance sustainable food production, suggests that industry regulators in Europe have known for years that glyphosate, originally introduced by American agricultural biotechnology giant Monsanto in 1976, causes birth defects in the embryos of laboratory animals.

Founded in 2009, Earth Open Source is a non-profit organization incorporated in the U.K. but international in scope. Its three directors, specializing in business, technology and genetic engineering, work pro-bono along with a handful of young volunteers. Partnering with half a dozen international scientists and researchers, the group drew its conclusions in part from studies conducted in a number of locations, including Argentina, Brazil, France and the United States.

Earth Open Source's study is only the latest report to question the safety of glyphosate, which is the top-ranked herbicide used in the United States. Exact figures are hard to come by because the U.S. Department of Agriculture stopped updating its pesticide use database in 2008. The EPA estimates that the agricultural market used 180 to 185 million pounds of glyphosate between 2006 and 2007, while the non-agricultural market used 8 to 11 million pounds between 2005 and 2007, according to its Pesticide Industry Sales & Usage Report for 2006-2007 published in February, 2011.

The Earth Open Source study also reports that by 1993 the herbicide industry, including Monsanto, knew that visceral anomalies such as dilation of the heart could occur in rabbits at low and medium-sized doses. The report further suggests that since 2002, regulators with the European Commission have known that glyphosate causes developmental malformations in lab animals.

Even so, the commission's health and consumer division published a final review report of glyphosate in 2002 that approved its use in Europe for the next 10 years.

As recently as last year, the German Federal Office for Consumer Protection and Food Safety (BLV), a government agency conducting a review of glyphosate, told the European Commission that there was no evidence the compound causes birth defects, according to the report.

The agency reached that conclusion despite almost half a dozen industry studies that found glyphosate produced fetal malformations in lab animals, as well as an independent study from 2007 that found that Roundup induces adverse reproductive effects in the male offspring of a certain kind of rat.

German regulators declined to respond in detail for this story because they say they only learned of the Earth Open Source report last week. The regulators emphasized that their findings were based on public research and literature.

Although the European Commission originally planned to review glyphosate in 2012, it decided late last year not to do so until 2015. And it won't review the chemical under more stringent, up-to-date standards until 2030, according to the report.

The European Commission told HuffPost that it wouldn't comment on whether it was already aware of studies demonstrating the toxicity of glyphosate in 2002. But it said the commission was aware of the Earth Open Source study and had discussed it with member states.

"Germany concluded that study does not change the current safety assessment of gylphosate," a commission official told HuffPost in an email. "This view is shared by all other member states."

John Fagan, a doctor of molecular and cell biology and biochemistry and one of the founders of Earth Open Source, acknowledged his group's report offers no new laboratory research. Rather, he said the objective was for scientists to compile and evaluate the existing evidence and critique the regulatory response.

"We did not do the actual basic research ourselves," said Fagan. "The purpose of this paper was to bring together and to critically evaluate all the evidence around the safety of glyphosate and we also considered how the regulators, particularly in Europe, have looked at that."

For its part, Earth Open Source said that government approval of the ubiquitous herbicide has been rash and problematic.

"Our examination of the evidence leads us to the conclusion that the current approval of glyphosate and Roundup is deeply flawed and unreliable," wrote the report's authors. "What is more, we have learned from experts familiar with pesticide assessments and approvals that the case of glyphosate is not unusual.

"They say that the approvals of numerous pesticides rest on data and risk assessments that are just as scientifically flawed, if not more so," the authors added. "This is all the more reason why the Commission must urgently review glyphosate and other pesticides according to the most rigorous and up-to-date standards."

Monsanto spokeswoman Janice Person said in a statement that the Earth Open Source report presents no new findings.

"Based on our initial review, the Earth Open Source report does not appear to contain any new health or toxicological evidence regarding glyphosate," Person said.

"Regulatory authorities and independent experts around the world agree that glyphosate does not cause adverse reproductive effects in adult animals or birth defects in offspring of these adults exposed to glyphosate," she said, "even at doses far higher than relevant environmental or occupational exposures."

While Roundup has been associated with deformities in a host of laboratory animals, its impact on humans remains unclear. One laboratory study done in France in 2005 found that Roundup and glyphosate caused the death of human placental cells. Another study, conducted in 2009, found that Roundup caused total cell death in human umbilical, embryonic and placental cells within 24 hours. Yet researchers have conducted few follow-up studies.

"Obviously there's a limit to what's appropriate in terms of testing poison on humans," said Jeffrey Smith, executive director of the Institute for Responsible Technology, which advocates against genetically modified food. "But if you look at the line of converging evidence, it points to a serious problem. And if you look at the animal feeding studies with genetically modified Roundup ready crops, there's a consistent theme of reproductive disorders, which we don't know the cause for because follow-up studies have not been done."

"More independent research is needed to evaluate the toxicity of Roundup and glyphosate," he added, "and the evidence that has already accumulated is sufficient to raise a red flag."

Authorities have criticized Monsanto in the past for soft-pedaling Roundup. In 1996 New York State's Attorney General sued Monsanto for describing Roundup as "environmentally friendly" and "safe as table salt." Monsanto, while not admitting any wrongdoing, agreed to stop using the terms for promotional purposes and paid New York state $250,000 to settle the suit.

Regulators in the United States have said they are aware of the concerns surrounding glyphosate. The Environmental Protection Agency, which is required to reassess the safety and effectiveness all pesticides on a 15-year cycle through a process called registration review, is currently examining the compound.

"EPA initiated registration review of glyphosate in July 2009," the EPA told HuffPost in a written statement. "EPA will determine if our previous assessments of this chemical need to be revised based on the results of this review. EPA issued a notice to the company [Monsanto] to submit human health and ecotoxicity data in September 2010."

The EPA said it will also review a "wide range of information and data from other independent researchers" including Earth Open Source.

The agency's Office of Pesticide Programs is in charge of the review and has set a deadline of 2015 for determining if registration modifications need to be made or if the herbicide should continue to be sold at all.

Though skirmishes over the regulation of glyphosate are playing out at agencies across the U.S. and around the world, Argentina is at the forefront of the battle.

THE ARGENTINE MODEL

The Earth Open Source report, "Roundup and birth defects: Is the public being kept in the dark?" comes years after Argentine scientists and residents targeted glyphosate, arguing that it caused health problems and environmental damage.

Farmers and others in Argentina use the weedkiller primarily on genetically modified Roundup Ready soy, which covers nearly 50 million acres, or half of the country's cultivated land area. In 2009 farmers sprayed that acreage with an estimated 200 million liters of glyphosate.

The Argentine government helped pull the country out of a recession in the 1990s in part by promoting genetically modified soy. Though it was something of a miracle for poor farmers, several years after the first big harvests residents near where the soy cop grew began reporting health problems, including high rates of birth defects and cancers, as well as the losses of crops and livestock as the herbicide spray drifted across the countryside.

Such reports gained further traction after an Argentine government scientist, Andres Carrasco conducted a study, "Glyphosate-Based Herbicides Produce Teratogenic Effects on Vertebrates by Impairing Retinoic Acid Signaling" in

2009.

The study, published in the journal Chemical Research in Toxicology in 2010, found that glyphosate causes malformations in frog and chicken embryos at doses far lower than those used in agricultural spraying. It also found that malformations caused in frog and chicken embryos by Roundup and its active ingredient glyphosate were similar to human birth defects found in genetically modified soy-producing regions.

"The findings in the lab are compatible with malformations observed in humans exposed to glyphosate during pregnancy," wrote Carrasco, director of the Laboratory of Molecular Embryology at the University of Buenos Aires. "I suspect the toxicity classification of glyphosate is too low."

"In some cases this can be a powerful poison," he concluded.

Argentina has not made any federal reforms based on this research and has not discussed the research publicly, Carrasco told HuffPost, except to mount a "close defense of Monsanto and it partners."

The Ministry of Science and Technology has moved to distance the government from the study, telling media at the time the study was not commissioned by the government and had not been reviewed by scientific peers.

Ignacio Duelo, spokesman for the the Ministry of Science and Technology's National Council for Scientific and Technical Research [CONICET], told HuffPost in an statement that while Carrasco is one of its researchers, CONICET has not vouched for or assessed his work.

Duelo said that the Ministry of Science is examining Carrasco's report as part of a study of the possible harmful effects of the glyphosate. Officials, he added, are as yet unable to "reach a definitive conclusion on the effects of glyphosate on human health, though more studies are recommended, as more data is necessary."

REGIONAL BANS

After Carrasco announced his findings in 2009, the Defense Ministry banned planting of genetically modified glyphosate-resistant soy on lands it rents to farmers, and a group of environmental lawyers petitioned the Supreme Court of Argentina to implement a national ban on the use of glyphosate, including Monsanto's Roundup product. But the ban was never adopted.

"A ban, if approved, would mean we couldn't do agriculture in Argentina," said Guillermo Cal, executive director of CASAFE, Argentina's association of fertilizer companies, in a statement at the time.

In March 2010, a regional court in Argentina's Santa Fe province banned the spraying of glyphosate and other herbicides near populated areas. A month later, the provincial government of Chaco province issued a report on health statistics from La Leonesa. The report, which was carried in the leftist Argentinian newspaper Página 12, showed that from 2000 to 2009, following the expansion of genetically-modified soy and rice crops in the region, the childhood cancer rate tripled in La Leonesa and the rate of birth defects increased nearly fourfold over the entire province.

MORE QUESTIONS

Back in the United States, Don Huber, an emeritus professor of plant pathology at Purdue University, found that genetically-modified crops used in conjunction with Roundup contain a bacteria that may cause animal miscarriages.

After studying the bacteria, Huber wrote Secretary of Agriculture Tom Vilsack in February warning that the "pathogen appears to significantly impact the health of plants, animals, and probably human beings."

The bacteria is particularly prevalent in corn and soybean crops stricken by disease, according to Huber, who asked Vilsack to stop deregulating Roundup Ready crops. Critics such as Huber are particularly wary of those crops because scientists have genetically altered them to be immune to Roundup -- and thus allow farmers to spray the herbicide liberally onto a field, killing weeds but allowing the crop itself to continue growing.

Monsanto is not the only company making glyphosate. China sells glyphosate to Argentina at a very low price, Carrasco said, and there are more than one hundred commercial formulations in the market. But Monsanto's Roundup has the longest list of critics, in part because it dominates the market.

The growth in adoption of genetically modified crops has exploded since their introduction in 1996. According to Monsanto, an estimated 89 percent of domestic soybean crops were Roundup Ready in 2010, and as of 2010, there were 77.4 million acres of Roundup Ready soybeans planted, according to the Department of Agriculture.

In his letter to the Agriculture Department, Huber also commented on the herbicide, saying that the bacteria that he's concerned about appears to be connected to use of glyphosate, the key ingredient in Roundup.

"It is well-documented that glyphosate promotes soil pathogens and is already implicated with the increase of more than 40 plant diseases; it dismantles plant defenses by chelating vital nutrients; and it reduces the bioavailability of nutrients in feed, which in turn can cause animal disorders," he wrote.

Huber said the Agriculture Department wrote him in early May and that he has had several contacts with the agency since then. But there's little evidence that government officials have any intention of conducting the "multi-agency investigation" Huber requested.

Part of the problem may be that the USDA oversees genetically modified crops while the EPA watches herbicides, creating a potential regulatory loophole for products like Roundup, which relies on both to complete the system. When queried, USDA officials emphasized that they do not regulate pesticides or herbicides and declined to comment publicly on Huber's letter.

A spokesman eventually conceded their scientists do study glyphosate. "USDA's Agricultural Research Service's research with glyphosate began shortly after the discovery of its herbicidal activity in the mid 1970s," said the USDA in a statement. "All of our research has been made public and much has gone through the traditional peer review process."

While Huber acknowledged his research is far from conclusive, he said regulatory agencies must seek answers now. "There is much research that needs to be done yet," he said. "But we can't afford to wait the three to five years for peer-reviewed papers."

While Huber's claims have roiled the agricultural world and the blogosphere alike, he has fueled skeptics by refusing to make his research public or identify his fellow researchers, who he claims could suffer substantial professional backlash from academic employers who received research funding from the biotechnology industry.

At Purdue University, six of Huber's former colleagues pointedly distanced themselves from his findings, encouraging crop producers and agribusiness personnel "to speak with University Extension personnel before making changes in crop production practices that are based on sensationalist claims."

Since it first introduced the chemical to the world in the 1970s, Monsanto has netted billions on its best-selling herbicide, though the company has faced stiffer competition since its patent expired in 2000 and it is reportedly working to revamp its strategy.

In a lengthy email, Person, the Monsanto spokeswoman, responded to critics, suggesting that the economic and environmental benefits of Roundup were being overlooked:

> The authors of the report create an account of glyphosate toxicity from a selected set of scientific studies, while they ignored much of the comprehensive data establishing the safety of the product. Regulatory agencies around the world have concluded that glyphosate is not a reproductive toxin or teratogen (cause of birth defects) based on in-depth review of the comprehensive data sets available.
>
> Earth Open Source authors take issue with the decision by the European Commission to place higher priority on reviewing other pesticide ingredients first under the new EU regulations, citing again the flawed studies as the rationale. While glyphosate and all other pesticide ingredients will be reviewed, the Commission has decided that glyphosate appropriately falls in a category that doesn't warrant immediate attention.

"The data was there but the regulators were glossing over it," said John Fagan of Earth Open Source, "and as a result it was accepted in ways that we consider really questionable."

CORNERING THE INDUSTRY?

Although the EPA has said it wants to evaluate more evidence of glyphosate's human health risk as part of a registration review program, the agency is not doing any studies of its own and is instead relying on outside data -- much of which comes from the agricultural chemicals industry it seeks to regulate.

"EPA ensures that each registered pesticide continues to meet the highest standards of safety to protect human health and the environment," the agency told HuffPost in a statement. "These standards have become stricter over the years as our ability to evaluate the potential effects of pesticides has increased. The Agency placed glyphosphate into registration review. Registration review makes sure that as the ability to assess risks and as new information becomes available, the Agency carefully considers the new information to ensure pesticides do not pose risks of concern to people or the environment."

Agribusiness giants, including Monsanto, Dow Chemical, Syngenta and BASF, will, as part of a 19-member task force, generate much of the data the EPA is seeking. But the EPA has emphasized that the task force is only "one of numerous varied third-party sources that EPA will rely on for use in its registration review."

The EPA is hardly the only industry regulator that relies heavily on data supplied by the agrochemical industry itself.

"The regulation of pesticides has been significantly skewed towards the manufacturers interests where state-of-the-art testing is not done and adverse findings are typically distorted or denied," said Jeffrey Smith, of the Institute for Responsible Technology. "The regulators tend to use the company data rather than independent sources, and the company data we have found to be inappropriately rigged to force the conclusion of safety."

"We have documented time and time again scientists who have been fired, stripped of responsibilities, denied funding, threatened, gagged and transferred as a result of the pressure put on them by the biotech industry," he added.

Such suppression has sometimes grown violent, Smith noted. Last August, when Carrasco and his team of researchers went to give a talk in La Leonesa they were intercepted by a mob of about a hundred people. The attack landed two people in the hospital and left Carrasco and a colleague cowering inside a locked car. Witnesses said the angry crowd had ties to powerful economic interests behind the local agro-industry and that police made little effort to interfere with the beating, according to the human rights group Amnesty International.

Fagan told HuffPost that among developmental biologists who are not beholden to the chemical industry or the biotechnology industry, there is strong recognition that Carrasco's research is credible.

"For me as a scientist, one of the reasons I made the effort to do this research into the literature was to really satisfy the question myself as to where the reality of the situation lies," he added. "Having thoroughly reviewed the literature on this, I feel very comfortable in standing behind the conclusions Professor Carrasco came to and the broader conclusions that we come to in our paper

"We can't figure out how regulators could have come to the conclusions that they did if they were taking a balanced look at the science, even the science that was done by the chemical industry itself."

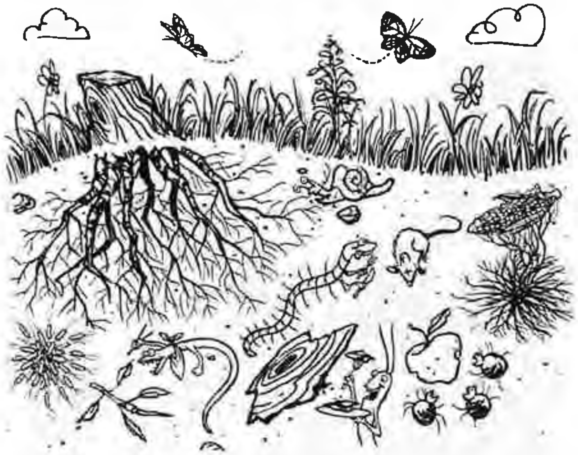
"Next time you hear a scientist asserting that gene splicing is safe, remind yourself that there is no scientific evidence for that statement. We are profoundly ignorant about what we are doing to the code that generates all life. And unfortunately some scientists, including those entrusted with public safety, are willing to lie".

—Donella H. Meadows, biophysicist
and environmentalist, Dartmouth
College

carbon out of the air as well. They feel 350 ppm is the most we can tolerate without extreme climate disruption. So we need to find a long term home for 50 ppm of carbon dioxide, which is 106 gigatons (Gt) of carbon.

But we can't store that carbon in the 70% of the planet that is covered with water. Carbon dioxide forms carbonic acid in water, which is already making the ocean too acid and killing many forms of sea life, including shellfish, corals, and plankton.

We must put the carbon in the soil, where the carbon came from and where it is needed. But let's understand the soil a little better.



Soil's Carbon Hunger and Photosynthesis

Soil is literally alive. It is full of bacteria, fungi, nematodes, protozoa, algae, and many, many other creatures. The huge appetites of these soil organisms for carbon means that they quickly consume all available organic matter in healthy soil.

But if carbon is so rapidly consumed in soil, then why does it not quickly vanish?

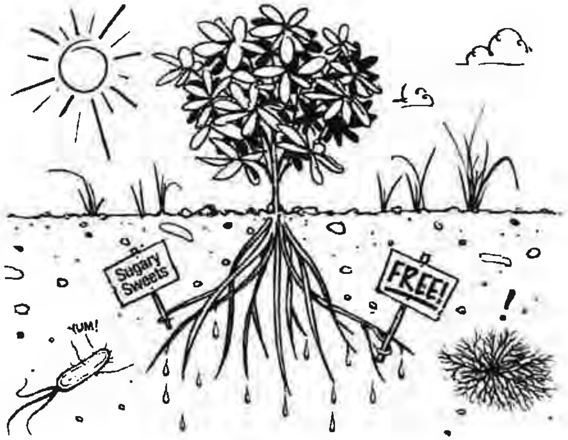
Because plants are constantly renewing the supply using their remarkable power to take carbon out of the air and put it into living matter. This, of course, is called photosynthesis.

The sheer scale of this process is impressive -- 15% of all carbon dioxide in the world's atmosphere moves through photosynthetic organisms each year!

All living things are carbon-based, and need to consume carbon to survive. If you can draw it out of thin air, as plants do, you have a commanding advantage. But even if you can't make carbon compounds, you must have them.

How else can soil microbes get carbon? They can "earn" it!

When plants photosynthesize and make carbohydrates they "leak" or exude a significant amount of these compounds as "liquid carbon" into the soil.



Root Exudates

Hungry soil organisms quickly show up to consume the tasty carbon-containing root exudates. But they soon want more. If a plant is strong it can exude more carbon.

So fungi find water and nutrients and transport them to the roots. Bacteria become chemists -- synthesizing hormones, fixing nitrogen, producing fungicides or antibiotics for the plants on demand. These relationships benefit both parties, at no cost.

Soil Aggregates

If you squeeze a handful of healthy soil, then release it, it should look like a bunch of peas. Those are soil aggregates. Inside those walls carbon exudates fuel lots of biological activity. Inside an aggregate it is moist and oxygen is scarce.These properties enable nitrogen-fixation and other biochemical activities to take place.

So, Can We Restore Enough Carbon to the Soil to Mitigate Weather Extremes in Time?

We know that 106 Gt of carbon will easily fit in the soil because that is where it came from. Land clearing and agriculture have brought out 136 Gt since 1750.

Many studies measure photosynthesis and soil carbon. They show:

- Perennial growing systems are great at restoring carbon.
- Row crop soils report lower carbon gains than pastures.
- Synthetic chemical fertilizers reduce or even eliminate soil carbon buildup. Manure and compost, however, do not.

The globe has 8.3 billion acres of grasslands and 3.8 billion acres of cropland. If each were managed using carbon-building practices, annually the grasslands could restore 21.6 Gt and the croplands 2.1 Gt. This totals 23.7 gigatons. Since we want to restore 106 Gt, we could do it in under 5 years!

Stable Carbon

Of course if we want to restore a lot of carbon to the soil it has to be done so that it won't be oxidized. One form of carbon that seems to remain stable for years is humus. It is composed of complex molecules containing carbon, but is not easily broken down by soil life. This is controversial, but many scientists believe that microbes produce humus in soil aggregates from liquid carbon. So, to restore carbon means not just adding organic matter to your soil. That will help microbes and can make crops flourish. But to build long term carbon, you need to do more.

Here are the practices that build long term carbon in soil:

Keep Soil Planted

Bare soil burns carbon, plants protect it by forming a barrier between air and soil. Growing plants are also your best protection against erosion. And plants add to soil carbon through their power of photosynthesis. Every square foot of soil that is left exposed – between rows of crops or in a fallow field – reduces your carbon bank account.

Minimize Tillage

Organic growers do lots of tillage for weed control. But it stirs up soil and oxidizes it. Tillage also rips up the fungal hyphae that carry water and nutrients to plant roots. Soil aggregates will be ruined by tillage, as will pore spaces in the soil that hold air and water.

Soil Carbon Restoration: Can Biology Do the Job?

by Jack Kittredge, NOFA/Mass policy director

How do we deal with greenhouse gas emissions and the resulting frequent weather extremes they have created? Clearly we must stop burning fossil fuels. But where can we put the carbon already in the air? There is only one practical approach -- to put it back where it belongs, in the soil. This will require all of us to help. We have written this short brochure to explain why and how carbon must be restored to the soil, and the advantages carbon-rich soils provide us.

Climate Change

Scientists believe that the cause of such unpredictable weather extremes is the buildup of manmade greenhouse gases in the atmosphere. Mostly carbon dioxide, but also other gases, they are emitted from soil and water into the atmosphere by natural processes. Those gases are also broken down by natural processes and returned to their sources in a continual cycle.

The concentration of a gas in the air is measured in units called "parts per million" (ppm). Throughout human history atmospheric carbon dioxide has stayed at roughly 280 ppm.

Human Disturbance of the Carbon Cycle

Since the dawn of agriculture some 12,000 years ago, however, human caused deforestation, land clearings and crop tillage have released excess carbon dioxide. With the burning of fossil fuels and industrialization of agriculture, these emissions have increased dramatically. Their level in the air now stands at 400 ppm.

We must curb our release of greenhouse gases. But that is not our only problem. Many scientists feel we must take

Cover Crops

Cover crops are essential to reduce or eliminate tillage, control weeds, and build soil carbon. Ideal cover crops are killed (by frost, mowing, crushing) before flowering, so they don't produce seeds. Their photosynthesis is an important source of soil carbon while living, and their biomass becomes available after they die. Legumes are important cover crops, as are long-rooted plants that bring nutrients from deep in the soil. Besides increasing soil carbon, cover crops also reduce nitrogen leaching, resist wind and water erosion, improve soil structure, increase water infiltration and reduce evaporation. Cover crop cocktails, mixes of various cover crop seeds, are excellent was to encourage biodiversity.

Diversity and Crop Rotation

Robust soil depends on a diverse soil microbial population. Microbial biomass is larger when legumes are included in the rotation. Animal manure is a valuable product of the small mixed farm, rich as it is in carbon and microbial biomass that inoculates the soil with microbes.

No Chemicals

Toxins like pesticides are lethal to many beneficial soil organisms, and the use of synthetic agricultural chemicals has been shown to be destructive of soil carbon. Water soluble fertilizers deplete soil organic matter by encouraging shallow roots, soil acidification, and obstructing the symbiosis between plants and soil microbes.

Pasture and Forests

Grazing on pasture is a highly effective way to restore soil carbon. Some people are concerned about ruminant animals giving off methane, a greenhouse gas. But in an ecological setting this is no problem as bacteria will quickly metabolize it. It is only when ruminants are away from biologically active soil or water, such as in feedlots or on soil where toxins have been applied, that ruminant methane emissions can be of concern. Some studies suggest woody plants are another way to deliver sizeable soil carbon gains.

Biochar

Soils enriched with char have a long term fertility that may be related to the protective habitats provided by char's internal spaces for microbes, or to its molecular structure, which creates a large capacity to retain ions of such minerals as calcium, potassium, and magnesium.

Benefits of Restoring Carbon to Soil

The advantages of restoring carbon your soil are not limited to removing carbon dioxide from the atmosphere.

Water - Increasing soil carbon builds aggregates, which in turn act as a sponge to enable soil to hold water, thus providing reserves in times when precipitation is low and a sink to soak up excess when it is high. This capacity to retain water also reduces the risk of erosion and crop loss.

Fungal Dominance - A high ratio of fungi to bacteria in soil is important to plant production. You have it if your soil smells mushroomy, not sour. It is the fungi that seek out and supply water and nutrients to plant roots as needed. Practices recommended here move soil toward fungal dominance.

Better Crops - Plants, like animals, have evolved complex defenses. Such abilities are strongest when the plant is healthy. Healthy plants also biosynthesize more of the volatile molecules and higher metabolites that produce the flavors and aromas of food crops. So restoring carbon to soils benefits all: farmers with larger yields, gardeners with tastier crops, and consumers with healthier food.

Conclusion

We have taken too much carbon from the soil, burned it, and sent it into the atmosphere as carbon dioxide. Even if we could stop burning fossil fuels tomorrow, the greenhouse gases already released will continue to raise global temperatures for many years.

We really have no alternative but to restore carbon to the soil. This can be done through biology, using a natural, time tested method. Farmers, gardeners, homeowners, landscapers, anyone who owns or manages land, can follow these simple principles and do both: restore carbon to the soil, and help rebuild the marvelous system that nature has put in place to renew our atmosphere -- while providing food, beauty and health for all creation.

This is a summary of a longer paper with sources. To read that or for further information on restoring soil carbon: www.nofamass.org/carbon

NOFA MASS

updated 8/14/15

JOIN THE 4‰ INITIATIVE

Soils for food security and climate

Building on solid, scientific documentation and concrete actions on the ground, the *"4‰ Initiative : soils for food security and climate"* aims to show that **food security and combating climate change are complementary** and to ensure that agriculture provides solutions to climate change. This initiative consists of a voluntary action plan under the **Lima Paris Agenda for Action (LPAA)**, backed up by a strong and ambitious research program.

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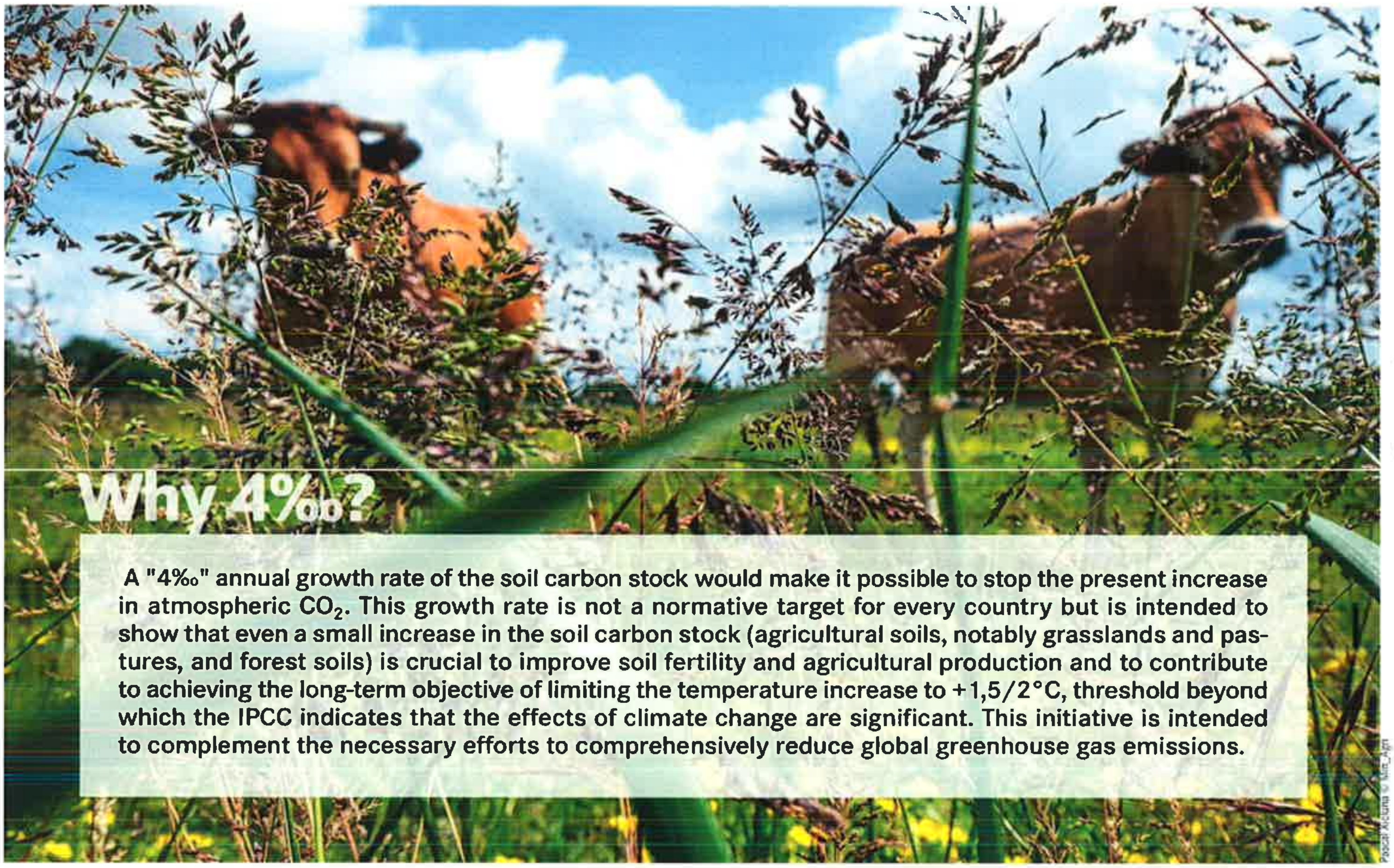

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Why 4‰?

A "4‰" annual growth rate of the soil carbon stock would make it possible to stop the present increase in atmospheric CO_2. This growth rate is not a normative target for every country but is intended to show that even a small increase in the soil carbon stock (agricultural soils, notably grasslands and pastures, and forest soils) is crucial to improve soil fertility and agricultural production and to contribute to achieving the long-term objective of limiting the temperature increase to +1,5/2°C, threshold beyond which the IPCC indicates that the effects of climate change are significant. This initiative is intended to complement the necessary efforts to comprehensively reduce global greenhouse gas emissions.

> ONE PRIORITY : AGRICULTURAL SOILS TO ENSURE FOOD SECURITY

One simple fact:

- Soil degradation poses a threat to more than 40% of the Earth's land surfaces and climate change is accelerating this rate of soil degradation and threatening food security.
- Disastrous consequences for food security and family farmers.

Our capacity to feed 9.5 billion people in 2050 in a context of climate change will depend in particular on our ability to keep our soils alive. The health of soils, for which sufficient organic matter is the main indicator, strongly controls agricultural production. Stable and productive soils affect the resilience of farms to cope with the effects of climate change.

Primarily composed of carbon, the organic matter in soils plays a role in four important ecosystem services: resistance to soil erosion, soil water retention, soil fertility for plants and soil biodiversity. Even small changes of the soil carbon pool have tremendous effects both on agricultural productivity and on greenhouse gas balance.

Maintaining organic carbon-rich soils, restoring and improving degraded agricultural lands and, in general terms, increasing the soil carbon, play an important role in addressing the three-fold challenge of food security, adaptation of food systems and people to climate change, and the mitigation of anthropogenic emissions. To achieve this, concrete solutions do exist and need to be scaled up.

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> ONE VISION : THE "4‰ INITIATIVE : SOILS FOR FOOD SECURITY AND CLIMATE"

The "4‰" Initiative aims to improve the organic matter content and promote carbon sequestration in soils through the application of agricultural practices adapted to local situations both economically, environmentally and socially, such as agro-ecology, agroforestry, conservation agriculture and landscape management.

- The Initiative engages stakeholders in **a transition towards a productive, resilient agriculture, based on a sustainable soil management and generating jobs and incomes, hence ensuring sustainable development.**
- **Thanks to its high level of ambition, this Initiative is part of the Lima-Paris Action Agenda and contributes to the sustainable development goals to reach a land-degradation neutral world.**
- All the stakeholders commit together in a **voluntary action plan** to implement farming practices that maintain or enhance soil carbon stock on as many agricultural soils as possible and to preserve carbon-rich soils. Every stakeholder commits on an objective, actions (including soil carbon stock management and other accompanying measures, for example index-based insurance, payment for ecosystem services, and so on), a time-line and resources.
- The Initiative aims to send out a strong signal concerning the potential of agriculture to contribute to the long-term objective of a carbon-neutral economy.

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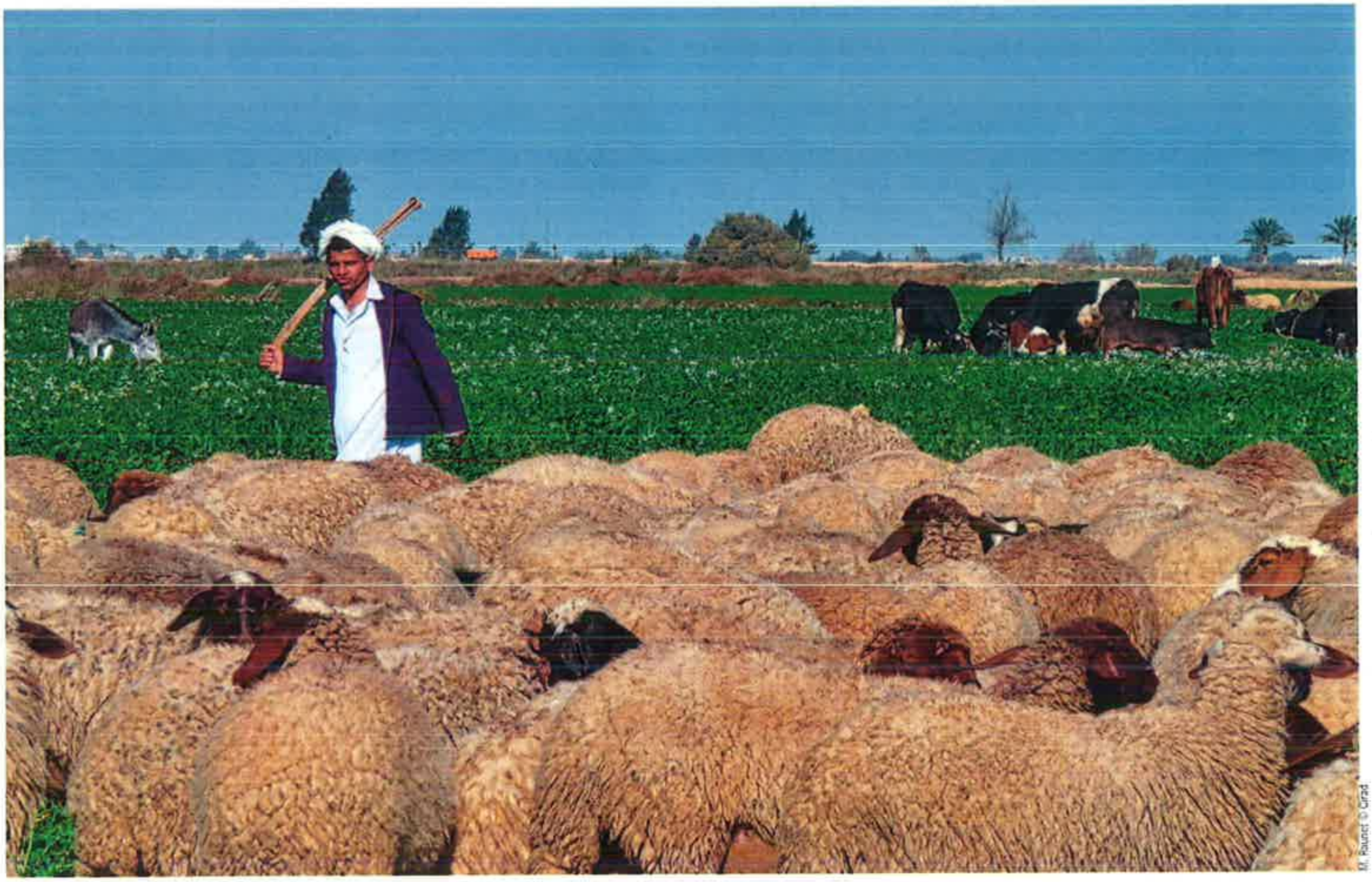

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> WHAT IS THE ADDED VALUE OF THE "4‰" INITIATIVE ?

The "4‰" Initiative aims to develop practical measures on the ground that benefit crop and livestock farmers, the first victims of land degradation, and more broadly for the whole world population.

This is a multi-partner initiative involving, in its first stage, all existing partnerships on soils and all stakeholders around two main strands of action:

a multipartner (state and non-state actors) program of actions for better management of soil carbon in order to combat poverty and food insecurity, while contributing to climate change adaptation and mitigation by:

- the implementation of agricultural practices at local level and management of environments favourable to the restoration of soils, to an increase in their organic carbon stock and to the protection of carbon-rich soils and biodiversity;
- the implementation of training and outreach programs to encourage such practices;
- the financing of projects to restore, improve and/or preserve carbon stocks in soils;
- the development and implementation of public policies and appropriate tools;
- the development of supply chains of soil-friendly agricultural products, and so on.

an international research and scientific cooperation programme – "Soil carbon and food security" focused on four complementary research themes:

- study of mechanisms and assessment of the potential for carbon storage in soils across regions and systems;
- performance evaluation of best farming practices for soil carbon and their impact on other greenhouse gases, on food security and on other regulation and production services;
- support of innovation and its promotion by appropriate policies;
- monitoring and estimating variations in soil carbon stock, especially at farmers level.

Joint action by all stakeholders should help attract new funding to the agricultural sector for adaptation to climate change, food security and emission mitigation, and encourage the implementation of adapted development policies and tools.

This Initiative also aims to strengthen existing synergies between the three Rio Conventions (the United Nations Framework Convention on Climate Change (UNFCCC), the United Nations Convention to Combat Desertification (UNCCD), the Convention on Biological Diversity (BDC), the Committee for Food Security (CFS), the Global Soil Partnerphip (GSP), and with the Sustainable Development Goals (SDGs) which will be adopted by the United Nations in September 2015. Desertification, climate change and loss of biodiversity can either interact to pose a threat or, on the contrary, to help bring appropriate solutions to sustainable development. The principles of the 4‰ initiative will fully support the World Soil Charter (1988/2015).

The objective of this Initiative is to encourage stakeholders (state and non-state actors) to get involved in a coordinated effort.

Follow-up to the initiative: the initiative's partners will share the actions they commit to undertaking and the results achieved through a platform. Exchange of views and stocktaking meetings will be held regularly in order to organise the follow-up to this initiative.

How to contribute?

- Governments and local authorities can undertake to:
  - ✔ implement training programs for farmers and agricultural counsellors which aim to enhance organic matter in soils;
  - ✔ establish adapted public policies and tools in particular to land tenure and sustainable soil management;
  - ✔ support financially development project that helps to develop carbon sequestration;
  - ✔ develop policies to supply agricultural products promoting sustainable management of soils through public procurement, where appropriate.

- Development Banks, Donors and private foundations may:
  - ✔ adopt an ambitious goal for development projects facilitating the dissemination and implementation of agricultural practices to increase, stabilize the rate of organic matter in the soil and preserve carbon-rich soils;
  - ✔ finance development projects, research projects, trainings or the implementation of MRV systems.

- International research can develop the four above-mentioned strands of action.

- Private companies may undertake to:
  - ✔ encourage the supply of products resulting from practices which are beneficial for the soil carbon, as they do against deforestation;
  - ✔ engage in soil rehabilitation projects.

- Farmers' and Food Producers' organizations can contribute to and encourage the adoption of new practices to store a larger amount of carbon while increasing soil fertility and resilience, in collaboration with research and NGOs.

- NGOs will have a key role to play in identifying, adapting and facilitating the dissemination of these good practices and ensuring that they meet producers' expectations, in collaboration with research and farmers' organizations.

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> MILESTONES

- **16 September 2015** International Conference on "*Agriculture and agricultural soils facing climate change and food security challenges: public policies and practices*" at the OECD
- **12-15 October 2015** Committee on Food Security in Rome - FAO
- **12-23 October 2015** UNCCD COP12 Desertification in Ankara
- **1 December 2015** COP21 in Paris : official launch of the "*4‰ Initiative : soils for food security and climate*" by signing a joint declaration between all stakeholders

Key figures

24 % of global soils are degraded at various levels, including 50 % of agricultural soils [source: Bai et al., 2013]

1 500 billion tonnes of carbon are stocked in soil organic matter, which is twice more carbon than atmospheric CO_2 [source : IPCC, 2013]

1,2 billion tonnes of carbon could be stocked every year in agricultural soils which represents an annual rate of 4‰ compared to the surface soil horizon [source : IPCC, 2014]

Every years crop production in Africa, Asia and South America could increase by **24/40** millions, by increasing soil organic matter by 1 tonne/ha [Lal , 2006]

1,2 billion USD is the economic loss in crop production due to soil degradation [FAO, 2006]

> HOW TO SUPPORT THE "4‰" INITIATIVE?

Who can join?

States, local authorities, companies, farmers organizations, NGO, research institutes can join.

How to participate?

1 Register at:
4p1000.dgpe@agriculture.gouv.fr

2 Register your commitments here:
http://climateaction.unfccc.int
(target, dedicated resources, calendar, area of land concerned, number of farmers concerned, and much else)

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More information

http://agriculture.gouv.fr/agriculture-et-foret/environnement-et-climat

Critical Reviews in Biotechnology

http://informahealthcare.com/bty
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informa healthcare

REVIEW ARTICLE

An overview of the last 10 years of genetically engineered crop safety research

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Abstract

The technology to produce genetically engineered (GE) plants is celebrating its 30th anniversary and one of the major achievements has been the development of GE crops. The safety of GE crops is crucial for their adoption and has been the object of intense research work often ignored in the public debate. We have reviewed the scientific literature on GE crop safety during the last 10 years, built a classified and manageable list of scientific papers, and analyzed the distribution and composition of the published literature. We selected original research papers, reviews, relevant opinions and reports addressing all the major issues that emerged in the debate on GE crops, trying to catch the scientific consensus that has matured since GE plants became widely cultivated worldwide. The scientific research conducted so far has not detected any significant hazards directly connected with the use of GE crops; however, the debate is still intense. An improvement in the efficacy of scientific communication could have a significant impact on the future of agricultural GE. Our collection of scientific records is available to researchers, communicators and teachers at all levels to help create an informed, balanced public perception on the important issue of GE use in agriculture.

Keywords

Biodiversity, environment, feed, food, gene flow, –omics, substantial equivalence, traceability

History

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Introduction

Global food production must face several challenges such as climate change, population growth, and competition for arable lands. Healthy foods have to be produced with reduced environmental impact and with less input from non-renewable resources. Genetically engineered (GE) crops could be an important tool in this scenario, but their release into the environment and their use as food and feed has raised concerns, especially in the European Union (EU) that has adopted a more stringent regulatory framework compared to other countries (Jaffe, 2004).

The safety of GE crops is crucial for their adoption and has been the object of intense research work. The literature produced over the years on GE crop safety is large (31 848 records up to 2006; Vain, 2007) and it started to accumulate even before the introduction of the first GE crop in 1996. The dilution of research reports with a large number of commentary papers, their publication in journals with low impact factor and their multidisciplinary nature have been regarded as negative factors affecting the visibility of GE crop safety research (Vain, 2007). The EU recognized that the GE crop safety literature is still often ignored in the public debate even if a specific peer-reviewed journal (http://journals.cambridge.org/action/displayJournal?jid=ebs) and a publicly accessible database (http://bibliosafety.icgeb.org/) were created with the aim of improving visibility (European Commission, 2010).

We built a classified and manageable list of scientific papers on GE crop safety and analyzed the distribution and composition of the literature published from 2002 to October 2012. The online databases PubMed and ISI Web of Science were interrogated to retrieve the pertinent scientific records (Table S1 – Supplementary material). We selected original research papers, reviews, relevant opinions and reports addressing all the major issues that emerged in the debate on GE crops. The 1783 scientific records collected are provided in .xls and .ris file formats accessible through the common worksheet programs or reference manager software (Supplementary materials). They were classified under the scheme given in Table 1, according to the major issues emerging from the literature. Beyond a numerical analysis of the literature, we provide a short explanatory summary of each issue.

General literature (GE gen)

Here we group all the reviews and critical comments offering a broad view of the issues concerning the release of the GE crops into the environment and their use as food and feed, including the regulatory frameworks and risk assessment procedures.

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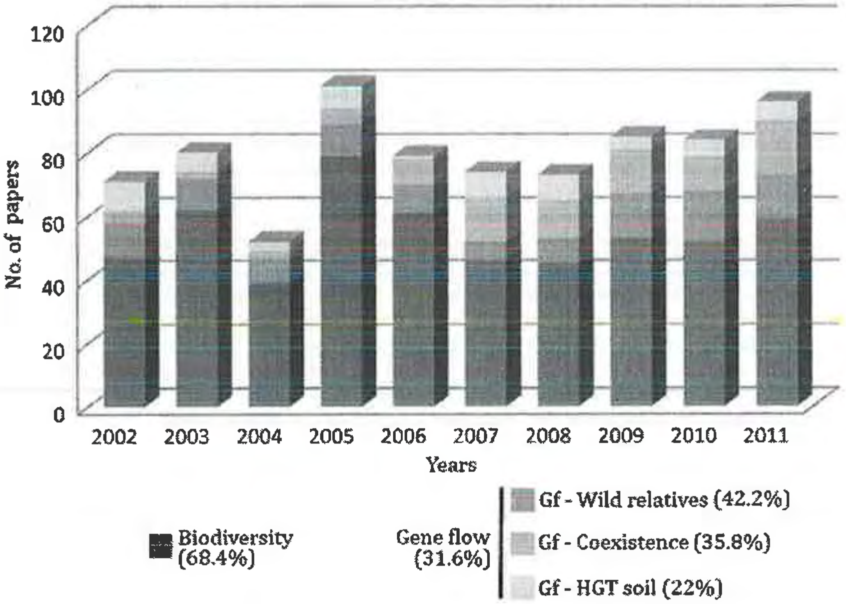
Table 1. Classification of 1783 scientific records on GE crop safety published between 2002 and 2012.

Topic	No. of papers	%*
General literature (GE gen)	166	9.3
Interaction of GE crops with the environment (GE env)	847	47.5
Biodiversity	579	32.5
Gene flow	268	15
Gf – Wild relatives	113	6.3
Gf – Coexistence	96	5.4
Gf – Horizontal gene transfer in soil	59	3.3
Interaction of GE crops with humans and animals (GE food&feed)	770	43.2
Substantial equivalence	46	2.6
Non-targeted approaches to equivalence assessment	107	6
GE food/feed consumption	312	17.5
Traceability	305	17.1

*Percentage of the total number of collected papers.

Figure 1. Main topics of the scientific papers belonging to the GE env group.



The weight of the **GE gen** section, in terms of number or records, is low in our database (9.3% – 166/1783) compared to **GE env** (47.5% – 847/1783) and **GE food&feed** (43.2% – 770/1783) (Table 1). The literature grouped in **GE gen** reflects the difference between the EU and the US regulatory frameworks: the former is based on the evaluation of the process by which the GE crop is obtained and the application of the precautionary principle, the latter is based on the evaluation of the product. The adoption of such different concepts resulted in the need for new legislation and new authorities in the EU, whereas in the US new regulations were integrated into the existing legislation and institutions (Jaffe, 2004).

Other countries have been inspired by these two systems in developing their own regulatory framework (Ramessar et al., 2008). As a result, the regulations on the release of GE crops into the environment and their use as food and feed are not uniform (Gómez-Galera et al., 2012; Jaffe, 2004; McHughen & Smyth, 2008; Ramessar et al., 2008). This lack of harmonization, and the frequent non-scientific disputes in the media that are not balanced by an effective communication from the scientific and academic world, greatly contribute to enhance the concerns on GE crops.

The EU funded more than 50 research programs in 2001–2010, for a total budget of 200 million euros, with the intent to gain new scientific evidence addressing the public concern on the safety of GE crops. A summary report of these programs highlighted that the use of biotechnology and of GE plants *per se* does not imply higher risks than classical breeding methods or production technologies (European Commission, 2010).

Interaction of GE crops with the environment (GEenv)

Biodiversity

Biodiversity preservation is unanimously considered a priority by the scientific community and society at large. This topic is predominant in **GE env** (68.4%) throughout the decade (Table 1; Figure 1). The literature is highly heterogeneous, since the potential impact of GE crops on biodiversity can be investigated at different levels (crop, farm and landscape) and different organisms or microorganisms (target and non-target) can be considered.

The GE crops commercialized so far are herbicide and/or pest resistant. Glyphosate tolerance obtained by expressing an *Agrobacterium tumefaciens* enolpyruvyl shikimate 3-phosphate synthase (EPSPS), and the production of insecticidal proteins derived from *Bacillus thuringiensis* (Bt), are by far the most widespread GE traits.

The literature considering the effects on biodiversity of non-target species (birds, snakes, non-target arthropods, soil macro and microfauna) is large and shows little or no evidence of the negative effects of GE crops (Carpenter, 2011 and references therein; Raven, 2010; Romeis et al., 2013). Two reviews about pest resistant GE crops published by Lövei et al. (2005, 2009) reported negative impacts on non-target arthropods; however, these reports have been criticized mainly for the statistical methods and the generalizations between crops expressing Bt proteins (commercialized), proteinase inhibitors (only a transgenic cotton line SGK321 present in the Chinese market) and lectins (not commercialized) (Gatehouse, 2011; Shelton et al., 2009). Negative impacts of Bt plants on non-target arthropods and soil microfauna have not been reported in recent papers (e.g. de Castro et al., 2012; Devos et al., 2012; Lu et al., 2012; Verbruggen et al., 2012 Wolfenbarger et al., 2011). Indeed, the positive impacts have been emphasised.

If we consider the effect of GE crops on the target species, weeds or pests, a reduction of biodiversity is obviously expected and necessary for the success of the crop. For instance, cases of area-wide pest suppression due to the adoption of Bt crops (where also the non-adopters of GE crops received beneficial effects), have been reported (Carpenter, 2011 and references therein). This is also the case of the UK Farm Scale Evaluations (FSE), a series of studies which highlighted that the adoption of a management system based on herbicide tolerant GE crops generally resulted in fewer weeds and weed seeds. These results have been used as proof of the negative environmental impact of herbicide tolerant crops, but indeed they demonstrate the effectiveness of such a management system (Carpenter, 2011 and references therein). On the other hand, higher reductions on biodiversity is generally expected with non-GE crops and herbicide/insecticide applications, because the chemicals used are often more toxic and persistent in the environment (Ammann, 2005).

Concerns have been raised about possible outbreak of resistant populations of target species due to the high selection pressures produced by the repetitive sowing of GE herbicide and pest resistant crops. Glyphosate resistant weeds have been reported (Shaner et al., 2012), as well as Bt resistant pests (Baxter et al., 2011; Gassman et al., 2011). Glyphosate tolerance appears more relevant because, while new Bt proteins are available which can be combined in strategies of stacking, or pyramiding, to reduce the risks of insect resistance (Sanahuja et al., 2011), it seems difficult to find herbicides equivalent to glyphosate in terms of efficacy and environmental profile; therefore, proper management of weed control is necessary (Shaner et al., 2012).

Gene flow

In an agricultural context, gene flow can be defined as the movement of genes, gametes, individuals or groups of individuals from one population to another, and occurs both spatially and temporally (Mallory-Smith & Sanchez Olguin, 2011). For instance, GE crop plants may be capable of surviving through seed or asexual propagules for years in the field, or they may be able to fertilize sexually compatible non-GE plants (non-GE crop or wild relative plants). The occurrence of gene flow may lead to the spread and persistence of transgenes into the environment or the market.

We have subdivided this topic into three subgroups: gene flow to wild relatives (Gf – Wild relatives), to other crops (Gf – Coexistence) or to microorganisms (Gf – Horizontal gene transfer in the soil). The literature on *Gene flow* makes up 31.6% of the **GEenv** literature and is clearly a ''hot topic'' because its share increased considerably after 2006 (Table 1; Figure 1).

Gf – Wild relatives

This topic represents 42.2% of the *Gene flow* literature (Table1; Figure 1). For estimating the gene flow to wild relatives, the knowledge of several factors is necessary: the reproductive biology of the GE crop, the presence or absence of sexually compatible wild relatives within the reach of GE pollen, and the reproductive biology and the fitness of any hybrid.

The formation of hybrids between GE crops and wild relatives is possible and documented (Londo et al., 2010; Mizuguti et al., 2010). Hybrid fitness determines the chance of transgene introgression, that is, permanent incorporation into the wild receiving population, which was reported in some cases (Reichman et al., 2006; Schoenenberger et al., 2006; Warwick et al., 2008). The risk of introgression should be evaluated case-by-case, considering the features of the transgene(s) incorporated into the GE crop.

The presence of spontaneous populations of GE canola with multiple herbicide resistance genes, probably due to multiple events of hybridization, has been reported (Schafer et al., 2011). Zapiola and Mallory-Smith (2012) recently described a new herbicide tolerant intergeneric hybrid of transgenic creeping bentgrass. Other cases have been reviewed (Chandler & Dunwell, 2008). Pest-resistant GE crops (i.e. Bt crops) may pose more risks than herbicide-resistant crops, because the introgression of a pest resistance transgene may confer fitness advantages to wild plants. Pest resistant wild plant populations may in turn exert selective pressure on the pest populations even in the absence of transgenic crops.

Strategies to mitigate the effect of the transgene(s) in pre- and post -hybridization phases have been proposed (e.g. male sterility, delayed flowering, genes that reduce fitness). However, none of them can be considered completely effective for transgene containment and complete segregation of GE crops is not possible. In any case, there is no evidence of negative effects of transgene introgression so far (Kwit et al., 2011).

It should be kept in mind that the gene flow between cultivated and wild species and its impact on biodiversity is an issue that exists independently of GE crops. The literature is rich in examples of natural invasive hybrids, disappearance of local genotypes (genetic swamping) and resistance to herbicides appearing in wild populations due to natural mutation (Kwit et al., 2011).

Gf – Coexistence

Gene flow from a GE to a non-GE crop can lead to an unwanted presence of the transgene in non-GE products. This issue involves not only the movement of pollen, but also the seeds that could remain in the field and give rise to volunteers, and the mechanical admixture of materials occurring during harvest, transportation and storage. The establishment of populations becoming partially wild (ferals) functioning as a natural reservoir of the transgene must also be considered, as well as the survival chances of the GE crops in the wild.

The coexistence issue goes beyond the matter of gene flow and involves several social and economic aspects, such as the manageability of complex agricultural scenarios where different agricultural systems (organic, conventional and biotech) coexist and a full traceability system is in force.

The collected records on coexistence account for 35.8% of the *Gene flow* literature and their number increased significantly after 2006 (Table 1; Figure 1). Even in the US, the coexistence issue is becoming actively discussed (http://www.gmo-compass.org/eng/news/548.docu.html).

Strategies of coexistence have been investigated for several species, such as maize (Devos et al., 2008; Langhof et al., 2010; Rühl et al., 2011), canola (Colbach, 2008; Gruber et al., 2005), soybean (Gryson et al., 2009), flax (Jhala et al., 2011), wheat (Foetzki et al., 2012), potato, cotton and sugar beet (European Commission, 2006). Maize has been the most intensively studied crop, followed by canola and wheat. Isolation distances, harvesting and post-harvesting practices have been proposed in order to avoid unwanted mixing of GE and non-GE-crop.

The feasibility of a coexistence plan is not only evaluated from a scientific point of view but also considering the extra economic costs due to the containment practices; such extra costs must find compensation in extra income from GE crops (Demont & Devos, 2008). In the EU, the scenario on coexistence is very poor currently, considering that only three GE crops are authorized for cultivation (MON 810 and T25 maize and ''Amflora'' potato), with only MON810 actually commercialized, and Spain accounting for 87% of the entire cultivated surface with GE crops (James, 2011).

Gf – Horizontal gene transfer in soil

Soil microorganisms may uptake the transgene(s) present into the GE crop. In fact, bacteria are naturally capable of acquiring genetic material from other organisms through horizontal gene transfer (HGT). To obtain a GE plant it can be necessary to introduce a gene that makes it possible to select the transgenic cells in tissue culture, by giving them an advantage over the non-transgenic cells. This is frequently achieved with bacterial antibiotic resistance genes that play the role of selectable marker genes (SMGs, recently reviewed by Rosellini, 2012). SMG presence in GE crops is not necessary in the field, and it has raised concerns about the spread of antibiotic resistance genes into the environment and their consumption as food or feed (see below).

The transfer of these genes to bacteria and the possible outbreak of ''super pathogenic bacteria'' resistant to antibiotics has been a matter of detailed investigation by the scientific community. The number of publications on this topic accounts for 22% of the *Gene flow* literature, with a stable presence in recent years (Table 1; Figure 1).

The results obtained so far clearly indicate that soil bacteria can uptake exogenous DNA at very low frequency (10^{-4} to 10^{-8}) in laboratory experiments (Ceccherini et al., 2003; de Vries et al., 2003), whereas experiments in the field did not show any evidence of HGT (Badosa et al., 2004; Demanèche et al., 2008, 2011; Ma et al., 2011). Moreover, in the unlikely event that soil bacteria acquired the resistance to an antibiotic among those currently used in the laboratory to select GE plants, this would not affect the population of natural antibiotic resistant bacteria already present in the soil (D'Costa, 2006; Forsberg et al., 2012) or imply any additional risk for human and animal health.

The substitution of antibiotic SMGs with plant-derived genes (Rosellini, 2011, 2012), their elimination (Ferradini et al., 2011 and references therein) and in general the elimination of any unwanted DNA sequence in the final GE crop is recommended (EFSA, 2011), as proposed with new approaches to plant genetic engineering such as the so-called intragenic (Nielsen, 2003; Rommens, 2004) or cisgenic (Jacobsen & Schouten, 2007) techniques.

Interaction of GE crops with humans and animals (GE food&feed)

Substantial equivalence

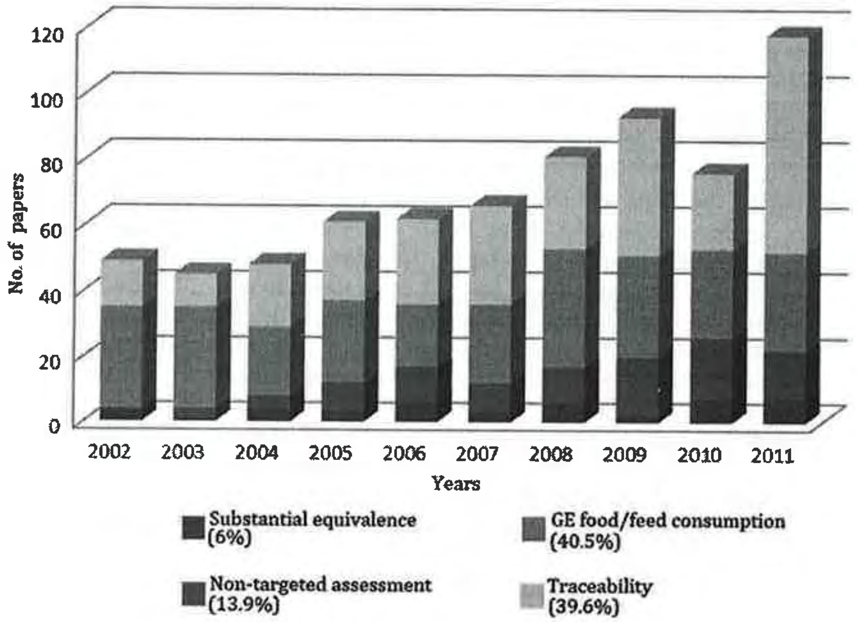
One of the crucial aspects of the risk assessment procedure for a GE crop is to verify if the insertion and/or the expression of the transgene produces alterations in the host organism. The concept of substantial equivalence implies that the GE crop be compared with an isogenic counterpart, that is, the same genotype without the transgene(s).

The demonstration of substantial equivalence is a two-step procedure. First, the GE crop is assessed for agronomic, morphological and chemical characteristics, such as macro- and micro-nutrients, anti-nutrients and toxic molecules. The results of this analysis will provide information on the necessity for further analysis of the nutritive value. Any difference which falls within the range of the normal variability for the crop is considered safe (Colquhoun et al., 2006; EFSA, 2011). This methodology has been agreed internationally (Codex, FAO, OECD, WHO) and involves the quantification of selected molecules, in a so-called ''targeted approach'' (Kok & Kuiper, 2003). If compositional differences are detected, then they have to be assessed with respect to their safety (Ramessar et al., 2007; EFSA, 2011).

The principle of substantial equivalence has been used for risk assessment of the GE crops commercialized so far (Kier & Petrick, 2008; König et al., 2004) and the results support the fact that these crops are equivalent to their non-transgenic counterparts (Parrot et al., 2010).

Concerns have been expressed about the efficacy of the method for detecting unintended effects. Field comparisons in multiple locations have been recommended in order to minimize the differences due to the environmental effects and large data collections have been created (www.cropcomposition.org).

Figure 2. Main topics of the scientific papers belonging to the GE food&feed group.



It is noteworthy that substantial equivalence represents an important common ground of the process-based and product-based regulatory frameworks. This clearly indicates a large consensus amongst scientists worldwide on GE crop evaluation (Kok et al., 2008). Substantial equivalence accounts for 6% of the scientific records collected in **GE food&feed** (Table 1; Figure 2). The literature is composed mainly by the publications produced by the companies that developed the GM cultivars, as part of the authorization process for commercialization. Public availability of the data on which these studies are based should be guaranteed.

Nontargeted approaches to equivalence assessment

The targeted approach to substantial equivalence assessment has an obvious limitation in the number of compounds that are analyzed. On the contrary, the so-called ''–omic'' approaches (transcriptomics, proteomics, metabolomics) can analyze a larger number of molecules (Kier & Petrick, 2008). Several GE crops were compared to their isogenic counterparts using –omic approaches and in some cases differences were observed. However, the interpretation of these results is difficult due to the non-homogeneity of the experimental designs. Moreover, the differences emerging from the –omic analyses have to be cleaned up from the environmental effects and their biological relevance weighted in terms of food and feed safety (Ricroch et al., 2011 and references therein).

It appears that the application of the –omics methods as standard procedure in the risk assessment of GE crop does not actually provide manageable information, and needs further development and validation. In this scenario, the substantial equivalence concept remains a robust and safe reference to determine the presence of unintended effects (European Commission, 2010). The weight of the nontargeted assessment topic increased significantly over the years, especially in 2009–2011 leading to a significant number of publications (13.9%) (Table 1; Figure 2).

GE food/feed consumption

The scientific records grouped under this topic are numerous and constitute 40.5% of the **GE food&feed** literature, clearly indicating the importance of the human health issues. The distribution over the year is uniform, but a peak was observed in 2008, probably due to the scientific fervors that followed the publication of experimental studies conducted by the private companies after 2006 (Table 1; Figure 2). According to the literature, the concerns about GE food/feed consumption that emerge from the scientific and social debates can be summarized as follows: safety of the inserted transgenic DNA and the transcribed RNA, safety of the protein(s) encoded by the transgene(s) and safety of the intended and unintended change of crop composition (Dona & Arvanitoyannis, 2009; Parrot et al., 2010).

Safety of the inserted transgenic DNA and the transcribed RNA

DNA. It is estimated that, with a normal diet, humans consume between 0.1 and 1 g of DNA/day from different sources (e.g. meat, vegetables) (Parrot et al., 2010). This DNA is partly digested, but it can also stimulate the immune-system or promote bacterial biofilm formation (Rizzi et al., 2012). The DNA sequences that drive the expression of the transgenes in the plant cell are generally derived from viruses or bacteria. Concerns have been expressed on the possibility that the transgenic DNA may resist the digestion process, leading to HGT to bacteria living in the gastrointestinal (GI) tract, or translocation and accumulation into the human body and food products from livestock animals. Some considerations can help to put this issue in context:

(a) transgenic DNA is enormously diluted by the total amount of ingested DNA (from 0.00006% to 0.00009%) and is digested like any other DNA (Parrot et al., 2010). In addition, food processing (e.g. baking, frying, boiling) usually results in DNA degradation (Gryson, 2010; Rizzi et al., 2012) further reducing the amount of intact DNA;

(b) HGT of transgenic DNA to GI bacteria of human and animals is estimated to be an extremely rare event, as confirmed by all the experiments conducted so far (Rizzi et al., 2012). In the unlikely case that this event occurs, the worst scenario is characterized by the HGT of antibiotic resistance genes to GI bacteria, making them resistant to clinical therapies. However, the antibiotic resistance genes found into GE crops today do not present any significant risk to human or animal health (Ramessar et al., 2007), and they are already naturally present into the environment and/or the human/animal GI (EFSA, 2011; Wilcks & Jacobsen, 2010).

(c) DNA fragments can be transferred across the GI barrier. This natural phenomenon has been demonstrated only for high-copy-number genes that have been detected in internal organs, tissues and blood of different animals and even in cow milk (Parrot et al., 2010; Rizzi et al., 2012; van de Eede et al., 2004 and references therein). In humans, the transfer through the GI tract of a high-copy-number gene from rabbit meat has been reported (Forsman et al., 2003).

(d) Transgenic DNA transfer through the GI tract has been reported in the literature in pig, lamb and rainbow trout (Chainark et al., 2006, 2008; Mazza et al., 2005; Sharma et al., 2006;), but in micro quantities and in the case of pigs and lambs with questionable reproducibility due to possible cross contamination (Walsh et al., 2011).

(e) In most studies conducted so far, no fragments of transgenic DNA were detected in any animal-derived products (ILSI, 2008). Only in one case, the presence of transgenic DNA in both ''organic'' and ''conventional'' cattle milk has been reported (Agodi et al., 2006).

(f) No evidence has been obtained to date that DNA absorbed through the GI tract can be integrated into the cells of the host organism and lead to a germ line transfer.

It can be concluded that transgenic DNA does not differ intrinsically or physically from any other DNA already present in foods and that the ingestion of transgenic DNA does not imply higher risks than ingestion of any other type of DNA (European Commission, 2010).

RNA. Along with the DNA also the corresponding transcribed RNAs are ingested and in general the content of DNA and RNA in foods are roughly comparable (Parrot et al., 2010). In the light of recent scientific evidence (Zhang et al., 2012a discussed below) concerns have been expressed about the potential effects that certain types of RNA (small double-strand RNAs, dsRNAs) introduced in some GE crops (e.g. virus resistant, altered oil composition) could have on human/animal health.

The function of such dsRNAs is not to be translated into proteins but to mediate gene regulation through a mechanism termed RNA interference (RNAi). The general mechanism of RNAi is conserved across eukaryotes and is triggered by different types of dsRNAs including small interfering RNA (siRNAs) and microRNAs (miRNAs) (Melnyk et al., 2011).

Recently, Zhang et al., (2012a) reported the first evidence of transfer, through the mouse GI tract, of a food-derived exogenous miRNA (MIR168a) naturally abundant in rice and previously detected also in human blood. This study highlights the unexpected resistance of the rice MIR168a to heat treatment during cooking and to digestion during the transit through the GI tract in the mouse. Moreover, the authors showed significant activity of the MIR168a on the RNAi-mediated regulation of a protein involved in the removal of low-density lipoprotein (LDL) in liver cells (Zhang et al., 2012a). This evidence is still the object of debate at the scientific level and a summary of the major issues are reported here:

(a) miRNAs are naturally present in both animal and plant derived foods/feeds and with a reported similarity to human genes (Ivashuta et al., 2009; Petrick et al., 2013);

(b) Petrick et al. (2013) pointed out that previous studies on feeding rats with rice (Zhou et al., 2011, 2012) failed to provide evidence on any alteration on LDL. However, such studies may be difficult to compare as they were conducted on another species of rodent and with different methodological approaches (e.g. different fasting of the animals and composition of the diet);

(c) although the systemic transmission of dsRNAs has been demonstrated in plants, worms and insects, such transport in mammals is still largely unknown (Melnyk et al., 2011). In humans, the presence of endogenous miRNAs has been documented in microvesicles circulating in the bloodstream and their role in intercellular communication is currently under investigation (Mittelbrunn & Sánchez-Madrid, 2012 and references therein);

(d) the results presented by Zhang et al. (2012a) are not in agreement with that documented in numerous clinical trials involving oral delivery of small RNA molecules. The stability of the dsRNAs in the GI tract and an efficient absorption through the mucosa in order to reach the active concentration of the molecule in the bloodstream, are still the limiting factors in this therapeutic approach (Petrick et al., 2013 and references therein);

(e) some miRNAs are active even at low concentrations and plant miRNAs seem to differ structurally from mammalian miRNAs (Yu et al., 2005; Zhang et al. 2012a; http://www.the-scientist.com/?articles.view/articleNo/31975/title/Plant-RNA-Paper-Questioned/);

(f) interestingly, Zhang et al. (2012b) detected the MIR168a sequence as predominant or sole plant miRNA in public animal small RNA datasets including insects. The authors point out that this may be an artifact due to the sequencing methodology employed (i.e. cross-contamination of the multiplexed libraries).

It can be concluded, that the RNA in general has the same ''history of safe use'' as DNA, since it is a normal component of the diet (Parrot et al., 2010). However, further investigations are necessary to clarify whether the evidence about the MIR168a is due to its unique properties or such conclusions can also be extended to other dsRNAs molecules contained in food/feed.

Safety of the proteins encoded by the transgenes

The expression of the introduced gene(s) leads to biosynthesis of one or more proteins. The ingestion of transgenic proteins has posed some questions about their possible toxic or allergenic effects in humans and animals. The safety of each transgenic protein is evaluated by means of the following analyses:

- bioinformatic analysis to assess the similarity with known allergens, toxic proteins and bioactive peptides;
- functional stability to pH and temperature;
- *in vitro* digestibility using simulate mammalian gastric fluid and simulated mammalian intestinal fluid, following the principle that a digested protein is less likely to be allergenic and absorbed in a biologically active form;
- protein expression level and dietary uptake, to estimate exposure of humans or animals to the protein;
- single dose (acute) toxicity testing and repeated dose (sub-chronic) toxicity testing in rodents using the purified transgenic protein, to predict *in vivo* possible toxic outcome in humans (Delaney et al., 2008; EFSA, 2008).

The results of these analyses are usually part of the documentation that GE crops developers submit to the competent authorities during the approval phase (risk assessment) that precede the commercialization of a GE crop. These data are not always made accessible by the companies or the competent authorities or published on peer-reviewed journals (Jaffe, 2004). However, as indicated by the significant increment of the publications after 2006, it seems that the GE crop developers acknowledged the necessity of an improved transparency (Domingo & Bordonaba, 2011). The experimental data collected so far on authorized GE crops can be summarized as follows:

(a) there is no scientific evidence of toxic or allergenic effects;
(b) some concern has been raised against GE corn MON 810, MON863 and NK603 (de Vendômois et al., 2009; Séralini et al., 2007, 2012), but these experimental results have been deemed of no significance (EFSA 2007, 2012; Houllier, 2012; Parrot & Chassy, 2009);
(c) only two cases are known about the potential allergenicity of transgenic proteins, the verified case of the brazil-nut storage protein in soybean, which has not been marketed (Nordlee et al., 1996) and the not verified case of maize Starlink (Siruguri et al., 2004);
(d) during the digestion process the proteins generally undergo degradation that leads to the loss of activity (Delaney et al., 2008);
(e) even though there are examples of some ingested proteins that are absorbed in minute quantities in an essentially intact form (e.g. ovalbumin, ovomucoid, β-lactoglobulin) (Kier & Petrick, 2008) or proteins that are hydrolyzed into smaller absorbed bioactive peptides (Udenigwe & Aluko, 2012), the consumption of transgenic proteins contained in the authorized GE crop does not result in any detectable systemic uptake (Kier & Petrick, 2008) and transgenic proteins are usually rapidly degraded and not detectable in animal derived products (e.g. milk, meat, eggs) (Ramessar et al., 2007);
(f) pre-screening of transgenic proteins through bioinformatic analyses contributes to avoid the introduction of potentially toxic, allergenic or bioactive proteins into food and feed crops (Delaney et al., 2008; Gibson, 2006; Ladics et al., 2011);
(g) the application of the concept of ''history of safe use'' to the choice the transgene donor organisms may increase intrinsic safety and simplify safety assessment procedures.

Safety of the intended and unintended changes of crop composition

Safety of the introduced change in the GE crop is usually evaluated during the determination of compositional equivalence (Section ''Substantial equivalence''). However, on a case-by-case basis, additional analyses can be requested, such as that of processed foods or feeds, nutritional equivalence and 90-day rodent feeding tests with whole GE food or feed (EFSA, 2008, 2011).

A useful distinction can be introduced here between GE crops modified for input traits (e.g. herbicide or insect resistance) and GE crops with enhanced nutritional characteristics (e.g. increased vitamin content). For the former, the experience suggests that, once the compositional equivalence has been verified, little can be added by the other types of analysis, and nutritional equivalence can be assumed (EFSA, 2011).

On the contrary, for GE crops with improved nutritional characteristics, the nutritional equivalence cannot be assumed, and a nutritional animal feeding test using rapidly growing animals (e.g. broilers) should be conducted to demonstrate the intended nutritional effect. The high sensitivity of rapidly growing animals to toxic compounds may also help to detect unintended effects. The 90-day rodent feeding test is generally performed when the composition is modified substantially or if there are indications of potential unintended effects.

Only GE crops modified for agronomic traits have been authorized for commercialization so far, with the only exception of the ''Amflora'' potato (event EH92-527-1), intended for industrial purpose but authorized also for feed and nonintended consumption (http://ec.europa.eu/food/dyna/gm_register/gm_register_auth.cfm?pr_id=39).

It is noteworthy that, at the moment, the route to the authorization of GE crops intended only for industrial purposes is not fully clarified by the legislation. However, the results of animal tests are routinely presented to the European safety assessment authorities, even if not explicitly required (http://www.gmo-compass.org/eng/safety/human_health/41.evaluation_safety_gm_food_major_undertaking.html).

Recently, Podevin & Jardin (2012) pointed out that the viral promoter P35S, isolated from the cauliflower mosaic virus (CaMV) and used in several GE crops to achieve strong and constitutive expression of the transgene/s, partially overlaps with the CaMV viral gene VI. In some long variants of the P35S promoter this could potentially lead to the production of a residual viral protein. The use of the short version of the promoter is therefore recommended, even if the bioinformatics analysis of the viral protein has not revealed any relevant similarity with known allergens (Podevin & Jardin, 2012).

An issue emerged about whether the combination of more GE traits in a single crop (GE stacks) may introduce changes that require additional safety assessment. Once safety of the single traits has been established independently, their combination should be evaluated in terms of stability, expression and possible interactions (EFSA, 2011). Weber et al. (2012) pointed out that GE stacks do not impose any additional risks in terms of transgene stability and expression, whereas attention should be focused only on the possible interactions between different traits.

Traceability

This is clearly a ''hot topic'' in **GE food&feed** (39.6%) (Table 1), with the publication rate after 2005 being high and constant (Figure 2). Traceability is defined in the EU General Food Law Regulation 178/2002/EC, inspired to the ISO standard, as the ''ability to trace and follow food, feed, food producing animals and other substances intended to, or expected to, be incorporated into food or feed, through all stages of production, processing and distribution''.

Traceability is a concept already widely applied to non-GE food/feed and it is not connected with their safety (Davison & Bertheau, 2007). It may include mandatory or voluntary labeling for the foods or feeds that contain or consist of GE crops or derived products. Labeling implies the definition of a threshold value, above which the food/feed is labeled according to the regulations in force.

The EU developed the most stringent regulatory framework for traceability of GE crops food/feed and derived products in the world. They have adopted mandatory labeling for unintentional presence of GE material in food or feed, with the lowest threshold value (0.9% based on the number of haploid genomes) compared to other countries (Davison & Bertheau, 2007; Ramessar et al., 2008). Labeling requires the detection and quantification of the GE food/feed or derived product in the tested food/feed or seeds or any other product when applicable. The scientific literature compiled about traceability largely deals with the following issues:

(a) sampling procedures – there are no universally acknowledged sampling procedures (Davison & Bertheau, 2007); this has been the object of a EU funded research programme (Paoletti et al., 2006);
(b) detection method – a large consensus has been established on qPCR (real-time quantitative PCR) -based methodologies that allows detection and quantification at the same time. Other experimental strategies and analytical methods have been proposed (e.g. microarray, Luminex XMAP), but they need further evaluation (Querci et al., 2010);
(c) definition of reference systems – the measurement unit of the GE product concentration depends on the unit used for the certified reference material (CRM) chosen for the analysis. At the moment, in the EU, mass fraction percentages are used for the CRMs, whereas a later recommendation from the EU suggested to use the ''copy number of transgenic DNA in relation to haploid genomes'', the unit of the legal threshold, so the development of suitable CRMs is necessary (Trapmann et al., 2009);
(d) detection of transgenes in mixtures composed by different ingredients, stacked transgenes and unauthorized events: all these issues require specific approaches and strategies have been proposed. The detection of the unauthorized events is very complex, because it could involve an already known transgene that did not receive authorization or a totally unknown GE event. Unfortunately, asynchronous authorization of GE crops or derived products in different countries does not improve this scenario: a higher degree of international harmonization would be beneficial (Holst-Jensen et al., 2012).

Conclusions

The technology to produce GE plants is celebrating its 30th anniversary. It has brought about a dramatic increase in scientific production over the years leading to high impact findings either in basic research (such as RNAi-mediated gene silencing) and applied research (GE crops), but the adoption of GE plants in the agricultural system has raised issues about environmental and food/feed safety.

We have reviewed the scientific literature on GE crop safety for the last 10 years that catches the scientific consensus matured since GE plants became widely cultivated worldwide, and we can conclude that the scientific research conducted so far has not detected any significant hazard directly connected with the use of GM crops. The analysis of the record list shows that the Biodiversity topic dominated, followed by Traceability and GE food/feed consumption, which contributed equally in terms of the number of records (Table 1; Figure 3).

It is noteworthy that the number of papers on Traceability has increased over the years, overcoming those on Biodiversity in 2011, clearly indicating an increasing demand for methods and protocols for transgene detection (Figure 3). The Gene flow issue also received increasing attention by the scientific community, as a response to the demands of the consumers connected with the coexistence of different productive systems (Figure 3).

It appears that knowledge on Gene flow and GE food/feed consumption would have benefited from a higher number of publications considering their high impact on both environmental and food/feed risk assessment. The difficulties of experimental design and, in the case of Gene flow, the public opposition to field trials, may have discouraged researchers, at least in the EU.

The literature about Biodiversity and the GE food/feed consumption has sometimes resulted in animated debate regarding the suitability of the experimental designs, the choice of the statistical methods or the public accessibility of data. Such debate, even if positive and part of the natural process of review by the scientific community, has frequently been distorted by the media and often used politically and inappropriately in anti-GE crops campaigns. In this regard, Houllier (2012) pointed out that, when

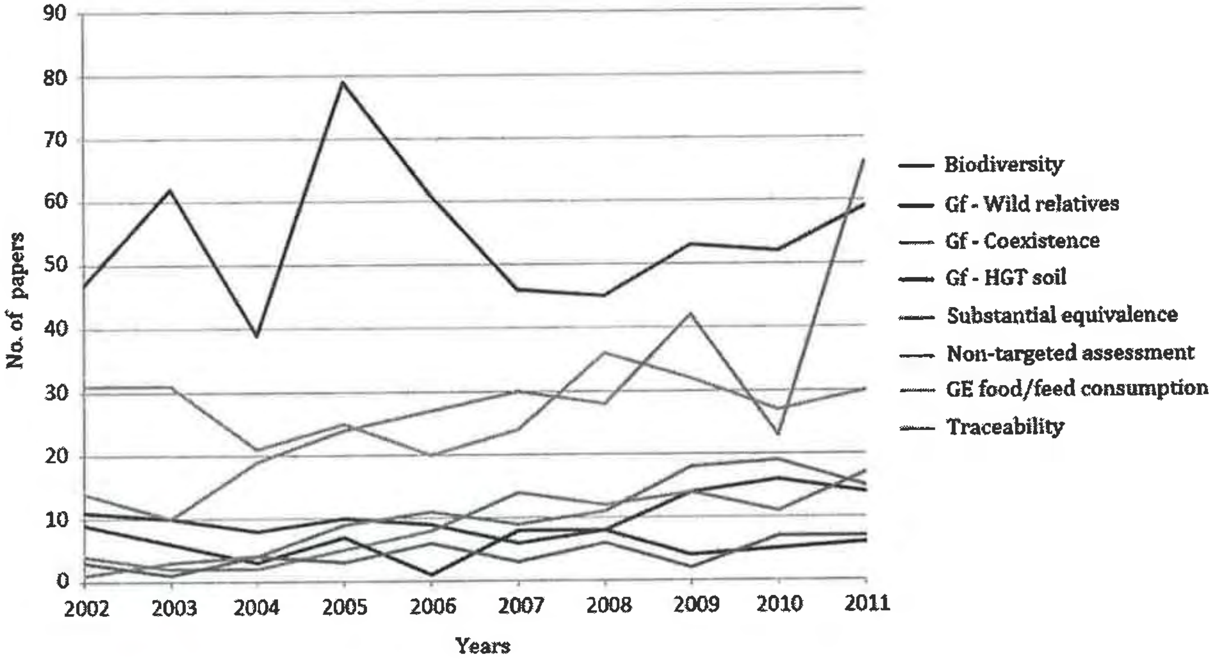


Figure 3. Distribution of the collected scientific papers. Records classified under the *General literature* are not shown.

dealing with ''hot issues'', researchers should take special care in following rigorous scientific standards, avoiding the publication of data not sufficiently peer reviewed by the scientific community.

It is interesting to note that the recent increase of scientific publications about Traceability and Non-targeted assessment (Figure 3) indicates considerable attention to the detection systems and the search for new safety evidence about a relatively low number of new approved GE crops. This likely reflects the consolidation of a situation in which the EU plays mainly the role of the importer of GE crop products from other countries, and enforces a stringent regulatory system.

In the EU, the regulatory burdens for GE crop approval are extremely heavy (Kalaitzandonakes et al., 2007), *de facto* excluding the public sector and minor crops from the development of GE technology. As a result, the number of experimental releases of GE crops is rapidly decreasing (Löchte, 2012) and even large companies are abandoning GE (Dixelius et al., 2012; Laursen, 2012). This scenario is the result of the interaction of complex sociological and psychological factors, risk/benefit ratios, political aspects and an unbalanced scientific communication.

All these factors have to be considered globally and taken into account in a constructive debate on whether the GE crops represent a strategic resource for the future. An improvement in the efficacy of the scientific communication to stakeholders, as clearly demonstrated in the case of the recent case of GE wheat field trials in the UK (Löchte, 2012), could have a significant impact on the future of agricultural GE.

We believe that genetic engineering and GE crops should be considered important options in the efforts toward sustainable agricultural production. Our collection of scientific records is available to researchers, communicators and teachers at all levels to help create an informed and balanced public perception on the hot issue of GE use in agriculture.

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Review

Assessment of the health impact of GM plant diets in long-term and multigenerational animal feeding trials: A literature review

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ABSTRACT

The aim of this systematic review was to collect data concerning the effects of diets containing GM maize, potato, soybean, rice, or triticale on animal health. We examined 12 long-term studies (of more than 90 days, up to 2 years in duration) and 12 multigenerational studies (from 2 to 5 generations). We referenced the 90-day studies on GM feed for which long-term or multigenerational study data were available. Many parameters have been examined using biochemical analyses, histological examination of specific organs, hematology and the detection of transgenic DNA. The statistical findings and methods have been considered from each study. Results from all the 24 studies do not suggest any health hazards and, in general, there were no statistically significant differences within parameters observed. However, some small differences were observed, though these fell within the normal variation range of the considered parameter and thus had no biological or toxicological significance. If required, a 90-day feeding study performed in rodents, according to the OECD Test Guideline, is generally considered sufficient in order to evaluate the health effects of GM feed. The studies reviewed present evidence to show that GM plants are nutritionally equivalent to their non-GM counterparts and can be safely used in food and feed.

Contents

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1. Introduction

In Europe, GM food and feed safety is assessed by the European Food Safety Authority (EFSA), which recommended that "the safety assessment of GM plants and derived food and feed follows a comparative approach, i.e. the food and feed are compared with their non-GM counterparts in order to identify intended and unintended (unexpected) differences which subsequently are assessed with respect to their potential impact on the environment, safety for humans and animals, and nutritional quality" (EFSA, 2008). With different methods, key elements of the assessment procedure such as molecular, compositional, phenotypic, and agronomic traits are analyzed in both the GM line and its near isogenic counterpart (EFSA, 2008). When "molecular, compositional, phenotypic, agronomic and other analyses have demonstrated equivalence of the GM food/feed, animal feeding trials do not add to the safety assessment" (EFSA, 2009; updated in EFSA, 2011). However, animal feeding studies may provide additional and useful information to complement safety and nutritional value assessments of whole GM food and feed, especially when unintended effects are suspected. The EFSA experts panel recommend that "the use of 90-days studies in rodents should be considered for the detection of possible unintended effects in food and feed derived from GM plants which have been more extensively modified in order to cope with environmental stress conditions like drought or high salt conditions, or GM plants with quality or output traits with the purpose to improve human or animal nutrition and/or health" (EFSA, 2008).

The protocols for *in vivo* toxicological studies are adapted from the 90-day rodent study as described in OECD Test Guideline No. 408 (Organisation for Economic Co-operation and Development, 1998), which defines the experimental material to test and the practical conditions used to test it (target animal species, housing, number of doses administered, gender and number of animals, etc.). The appropriate methods used to measure phenotypic responses (body weight, food consumption, clinical biochemistry, etc.) in test animals throughout the test are also provided. Over the last few decades, these parameters have been refined for an improved toxicological assessment of low molecular weight xenobiotics such as drugs, pesticides or additives, and serve as a foundation for the evaluation of GM-based food or feed. While feeds are identical between animal groups (treated or control) in the normal 90-day rodent study, adaptation of this test to food safety studies raises many specific questions on the strengths and weaknesses of such tests. For example, to assess the potential health effects of GM-based food or feed, 33% GM animal feed is usually incorporated (see recommendations of Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, ANSES, 2011). Feeding experiments using rodent models allow whole GM material to be tested, this assessment being motivated by either a modification in the GM plant composition, or by indications of potential unintended effects (EFSA, 2006, 2008). More precisely, 90-day animal feeding studies do not search for one particular effect of a given molecule, but are supposedly designed to detect most of the changes that may occur, including those potentially generated by the genetic modification as well as those resulting from a compositional change which is directly or not linked to the transgene. Thus, these studies might appear too wide and insufficient to detect weak effects, as EFSA (2008) has already stated "*It is unlikely that substances present in small amounts and/or with a low toxic potential will result in any observable unintended effects*". The key point is that in the case of a chemically defined molecule for which human exposure is very low, one can increase its dose in the classical 90-day feeding studies, whereas one cannot do so with a food or with a quantitatively important constituent in the diet.

Moreover EFSA (2008) states that "the subchronic, 90-day rodent feeding study is not designed to detect effects on reproduction or development, other than effects on adult reproductive organ weights and histopathology. Thus, in some cases, testing of the whole food and feed beyond a 90-day rodent feeding study may be needed. In cases where structural alerts, indications from the subchronic study or other information on the whole GM plant derived food and feed are available that suggest the potential for reproductive, developmental or chronic toxicity, the performance of such testing should be considered".

Possibly, some 90-day rodent feeding studies may be insufficient to reveal the presence of late effects in animals. Therefore, long-term studies, namely those performed for longer than 90 days, as well as multigenerational studies, will evaluate whether unintended effects are only detected by such studies and whether long-term studies have different findings than 90-day studies. In this paper we address the following question: Do recently published studies on long-term effects of GM plants, i.e. studies significantly longer than the 90-day sub-chronic tests, as well as multigenerational studies, present new evidence indicative of some adverse effects? The goal of this review is to compile and discuss the results of recently published studies on long-term effects as well as multigenerational studies for GM plants on which 90-day studies are also available. Twelve long-term and twelve multigenerational studies are examined. This review highlights the knowledge generated by these recently published studies to evaluate the possible existence of long-term health effects. The necessity to renew the current regulatory designs will also be discussed.

2. Material and methods

For this systematic review, 55 peer-reviewed references were identified from our database ('BergeRicrochGMLibrary'; Ricroch et al., 2010), which includes 32,000 references on transgenic plants, collected since 1996, using the keywords "*GM plant*", "*health*", "*long term*" and "*multigenerational*". Studies that were neither multigenerational nor longer than 96 days (OECD protocols + 10%), nor concerning animal feeding trials were discarded.

The duration and number of generations in every study concerned were identified. The one-generation long-term studies were manually sorted from the multigenerational ones. All 90-day rodent studies using the same GM line are referenced in Table 1. Twelve studies using a one-generation design, and longer

Table 1
90-day Safety Studies Performed on Rats with GM Plant Derived Foods.

Plant	Trait	Reference	Duration (in days)	Parameters
Maize	CP4 EPSPS (*Agrobacterium*)	Hammond et al. (2004)	90	Feed consumption. Body weight gain, organ weights. Blood cell count, blood chemistry, urine chemistry. Histopathology
Maize	Cry3Bb1 endotoxin (*Bacillus thuringiensis* var kumamotoensis)	Hammond et al. (2006a)	90	Feed consumption. Body weight gain, organ weights. Blood cell count, blood chemistry, urine chemistry. Histopathology
Maize	Cry1Ab endotoxin (*Bacillus thuringiensis* var kurstaki)	Hammond et al. (2006b)	90	Feed consumption. Body weight gain, organ weights. Blood cell count, blood chemistry, urine chemistry. Histopathology
Maize	Cry1F endotoxin (*Bacillus thuringiensis* var aizawai) and phosphinothricin acetyltransferase (*bar* gene, Streptomyces viridochromogenes)	Mackenzie et al. (2007)	90	Feed consumption, body weight. Clinical pathology (serum, blood, urine). Anatomical pathology (organ weights, histopathology)
Maize	Cry34Ab1 and Cry35Ab1 endotoxins (*Bacillus thuringiensis* Berlinerstrain PS149B1) and phosphinothricin-acetyltransferase (*bar* gene, *Streptomyces viridochromogenes*)	Malley et al. (2007)	90	Feed consumption/efficiency, body weight/gain. Neurobehavioural and ophthalmological examinations. Clinical pathology (hematology, clinical chemistry, coagulation, and urinalysis). Pathology (organ weights and gross, microscopic pathology)
Rice	GNA lectin (*Galanthus nivalis*)	Poulsen et al. (2007)	90	Feed and water consumption, body weight, organ weights. Blood cell count, blood chemistry, blood immunochemistry, splenocyte proliferation. Intestinal microbiology. Histopathology
Rice	Cry1Ab endotoxin (*Bacillus thuringiensis* var kurstaki)	Wang et al. (2002)	98	Feed consumption. Body weight, organ weights. Blood chemistry, blood cell count. Histopathology
Soybean	CP4 EPSPS (*Agrobacterium*)	Zhu et al. (2004)	91	Feed consumption. Body weight, organ weights. Blood chemistry, blood cell count. Histopathology

than 90 days (Table 2), and 12 multigenerational studies (Table 3) were finally considered in this meta-analysis. Studies which involved the examination of organs are summarized in Table 4.

3. Results

3.1. 90-day feeding studies

Based on the EFSA (2008) review, we referenced the 90-day studies using GM feed for which long-term or multigenerational studies were conducted (Table 1). Eight 90-day feeding trials conducted using transgenic maize, rice and soybean were performed on rats. The five studies using maize (Hammond et al., 2004, 2006a,b; Mackenzie et al., 2007; Malley et al., 2007) found no differences between the diets containing GM material and the ones which did not. These studies concluded that the maize grain tested were as safe and nutritious as existing commercial maize hybrids. The two studies using rice (Poulsen et al., 2007; Wang et al., 2002) found statistically significant differences between the control and the GM diet groups. However, in both studies most of these observed differences were within the normal biological range and were not indicative of harm. Wang et al. (2002) concluded that the Bt rice flour had no toxic effect on rats. Poulsen et al. (2007) did not conclude on the safety of the GNA lectin-producing rice tested even though no adverse effects were observed: "*In the present study, several significant differences were observed between rats fed diets with genetically modified and parental rice. Most of these differences appeared to be related to the increased water intake of the rats fed GM rice, which probably relates to the GNA lectin content, but none of the effects were considered to be adverse*". Another study using herbicide-tolerant soybean (Zhu et al., 2004) reported no significant difference and therefore concluded that no adverse effects were observed. In summary, analysis of the results from these 90-day rodent feeding trials with GM maize, rice and soybean did not reveal any indication of adverse effects.

3.2. Long-term studies

The studies discussed below were carried out for periods longer than 90–96-days and were intended to assess potential hazards that could arise in food or feed derived from GM plants. Studies involving long-term feeding but in which the animals were mated will be examined in the section 'multigenerational studies'. The model mainly used in these studies is rat. However some groups used mice, cows and fish. A variety of criteria have been assessed such as body and organ weight measurements, hematological analyses, enzyme activities, macro- and microscopic (histopathological) observations of particular organs and tissues, and detection of transgenic DNA. The duration of GM-based diet feeding in these studies varies from 182 days (26 weeks) to 728 days (104 weeks).

The studies presented here are listed in the Table 2 in which the various parameters considered and results are reported. Information on transgenic events and cultivars, animal model, diet and number of individuals and groups were considered as crucial parameters for the quality of the experimental protocols. To emphasize the differences that can exist in certain studies, results were presented in three columns: facts, authors' interpretation and the interpretation of others ("Criticisms" column). The following paragraphs discuss the most important parameters that varied and results obtained in the most relevant studies compiled in Table 2.

3.2.1. Insect-resistant maize

No long-term rodent studies are available for GM maize. However, a study in which 36 cows in total were fed a feed based on Bt-maize (event MON810) containing the protein Cry1Ab, or its isogenic not genetically modified counterpart for over 25 months covering two consecutive lactations has been published recently (Steinke et al., 2010). The diets from both the transgenic and isogenic lines were nutritionally equivalent: chemical composition in macronutrients and the estimated net energy content were not different. During this investigation the same cows were submitted to a second lactation and again fed the transgenic line; lactose concentrations in milk were higher and body weight and back fat thickness were lower when compared to cows fed the diet based on the isogenic (non-GM) line. In both groups, the milk yield (i.e. 23.9 and 29.2 kg/cow/d in the first and the second lactation, respectively, for cows fed non-GM maize; 23.7 and 28.8 kg/cow/d in the first and the second lactation, respectively, for cows fed GM maize) was not affected by dietary treatment. Only very small differences in fat, protein and urea concentrations were found, with cows fed the MON810-based diet producing higher levels of these constituents. However, according to the authors, the absolute

Table 2
Impact of GM plant diets in long term studies.

Plant	Trait	Reference and funding	Species	Duration	Parameters	Group (n = number of individuals per group)	Main findings	Authors' interpretation of results	Criticisms
Maize	Bt-MON810 containing Cry1Ab protein	Steinke et al. (2010). Not specific funding mentioned	Dairy cows	25 months (100 weeks)	Milk composition and yield	2 groups (n = 18); in total 36 individuals.	Small changes in milk composition and body weight in GM-fed cows but fall within normal ranges	Safe, no long term effects. Bt-MON810 and its isogenic control are equivalent	
Soybean	Glyphosate-tolerant soybean (event not mentioned)	Daleprane et al. (2009a). State of Rio de Janeiro Research Assistance Foundation (FAPERJ). National Council for Scientific and Technological Development (CNPq)	Rats	455 days (65)	Growth. Blood composition	3 groups (n = 10 male rats); in total 30 individuals.	GM group and organic group weight the same, higher than control group. Lower protein intake in control group. Growth, albumin, serum similar in all three groups	No differences between non-GM and GM groups. Soybean can be used in animal diets as a protein source	No isogenic line used
Soybean	Glyphosate-tolerant soybean (event not mentioned)	Daleprane et al. (2010). Brazilian foundations FAPERJ and CNPq	Rats	455 days (65)	Aorta wall tissue. Cholesterol, triaclyglycerol, insulin, glucose and testosterone	3 groups (n = 10 male rats); in total 30 individuals.	Lower body weight and fat mass in control group	No differences observed between non-GM and GM groups in all parameters. Non-GM and GM groups substantially equivalent	No isogenic line used
Soybean	Glyphosate-tolerant soybean (event not mentioned)	Sakamoto et al. (2007) (complete paper in Japanese). Tokyo Metropolitan Institute of Public Health	Rats	26 and 52 weeks	Growth. Feed intake. Organ weight. Hematology, serum	3 (number of individuals not precised)	Differences in growth, feed intake, organ weight between groups. Body weight and feed intake similar between GM and non-GM soybean	Safe, no long term effects	No isogenic line used, event not precised, number of individuals not precised, full article not available in English
Soybean	Glyphosate-tolerant soybean (event not mentioned)	Sakamoto et al. (2008) (complete paper in Japanese). Tokyo Metropolitan Institute of Public Health	Rats	104 weeks	Growth. Feed intake. Organ weight. Hematology, serum	3 (number of individuals not precised)	Differences in growth, feed intake, organ weight between groups. Body weight and feed intake similar between GM and non-GM soybean	Safe, no long term effects	No isogenic line used, event not precised, number of individuals not precised, full article not available in English
Soybean	Glyphosate-tolerant soybean (CP4 EPSPS)	Malatesta et al. (2002a). Not specific funding mentioned	Mice	240 days (30)	Ultrastructural morphetrical and immunocytochemical analyses of hepatocytes nuclei	2 groups (n = 12 female mice); in total 24 individuals.	Irregularly shaped nuclei, higher number of nuclear pores, numerous small fibrilla centres and abundant dense fibrillar component, nucleoplasmic and nuclear splicing factor more abundant in GM fed mice	Higher metabolic rate and molecular trafficking. Influence GM soybean intake on hepatocyte nuclear features in young and adult mices (mechanisms unknown)	No isogenic line used. Soybean not grown under the same conditions. International standards not reached. See text
Soybean	Glyphosate-tolerant soybean (CP4 EPSPS)	Malatesta et al. (2002b). Not specific funding mentioned	Mice	240 days (30)	Histocytochemistry pancreatic acinar cells	2 groups (n = 12 female mice); in total 24 individuals.	No differences in body weight and no macroscopic changes in the pancreas. No structural modifications but quantitative changes in some cellular constituents. Reduction	A diet containing significant amounts of GM food seems to influence the zymogen synthesis and processing in pancreatics incinar cells (reasons remain unknown)	No isogenic line used. Soybean not grown under the same conditions. International standards not reached. See text

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Table 2 (*continued*)

Plant	Trait	Reference and funding	Species	Duration	Parameters	Group (n = number of individuals per group)	Main findings	Authors' interpretation of results	Criticisms
							of α-amylase synthesis		
Soybean	Glyphosate-tolerant soybean (CP4 EPSPS)	Malatesta et al. (2003). Not specific funding mentioned	Mice	240 days (30)	Ultrastructural morphetrical and immunocytochemical analyses of pancreatic acinar cells nuclei	.2 groups (n = 12 female mice); in total 24 individuals.	Decrease of the shape index and the fibrillar centres density and increase of the pored density, the perichromatin granule density, the percentage of fiibrillar centres in GM-fed mice. Lower labellings for the nucleoplasmic splicing factors	A diet containing significant amounts of GM food seems to influence the pancreatic metabolisms	No isogenic line used. Soybean not grown under the same conditions. International standards not reached. See text
Soybean	Glyphosate-tolerant soybean (CP4 EPSPS)	Vecchio et al. (2004). Italian Ministry of University and Research and by the Fondo di Ateneo per la Ricerca, Pavia University	Mice	240 days (30)	Enzyme chemistry of serum, liver, and pancreas	2 groups (n = 12 female mice); in total 24 individuals.	Enlarged vesicles of the smooth endoplasmic reticulum, Decrease in the number of nuclear pores. Reduced labelling during the 2–8 month interval. Increase in perichromatin granules in Sertoli cells and in spermatocytes of GM fed mice	A transient transcriptionnal decrease during the 2–8 months intervall. Most of the effects reversible. Causes of the alteration not established, especially because glyphosate residues might influence transcriptionnal process	No isogenic line used. Soybean not grown under the same conditions. International standards not reached. See text
Soybean	Glyphosate-tolerant soybean (CP4 EPSPS)	Malatesta et al. (2008). Italian Ministry of Health	Mice	2 years (104)	Histocytochemistry of hepatocytes	2 groups (n = 10 female mice); in total 20 individuals.	Different expression of proteins related to hepatocyte metabolism, stress response, calcium signalling and mitochondria in GM-fed mice. Indications of reduced metabolic rate in GM-fed mice	GM soybean can influence some liver features during ageing	No isogenic line used. Soybean not grown under the same conditions. International standards not reached. See text
Soybean	Glyphosate tolerant soybean (event not mentioned)	Sissener et al. (2009). Norwegian Research Council	Salmons	7 months (28)	Growth. Body weight. Organ development. Plasma enzymes and nutrients. Differential white blood cell count	3 groups (n = 640); in total 1920 individuals	Mid intestine smaller in GM-fed group. Triaclyglcerol increased in GM-fed group. No growth differences between groups	Mid intestine smaller in GM-fed group. Triaclyglcerol increased in GM-fed group. No growth differences between groups	Safe, no term effects. Differences seen due to soybean cultivar non-GM diet
Rice	7Crp#10 (*7Crp* gene derived from cedar pollen Cryj I and Cryj II allergen protein genes)	Domon et al. (2009). Not specific funding mentioned	Macaques	26 weeks	Gross Necropsy. Histopathology and Absolute and Relative Organ Weights. Blood composition	3 groups (n = 6; three males and three females); in total 18 individuals.	With few exceptions, no significant differences in hematological or biochemical values between them. Neither pathological symptoms nor histopathological abnormalities observed	With few exceptions, no significant differences in hematological or biochemical values between them. Neither pathological symptoms nor histopathological abnormalities observed	No adverse effects on behavior or body weight, hematological and biochemical variables. No pathological symptoms or histopathological abnormalities

Table 3
Impact of GM plant diets in multigenerational studies.

Plant	Trait	Reference & Funding	Species	Duration	Parameters	Group (n = number of individuals per group)	Main Findings	Authors' Interpretation of Results	Criticisms
Maize	Bt11	Brake et al., 2003. No specific funding mentioned	Broiler chickens	42 days (6 weeks)	Survival. Body weight. Feed efficiency and carcass	4 groups (100); 2 groups (200 male individuals) and 2 groups (200 female individuals), in total 400 individuals. 3 generations	No differences in all parameters	Safe, no multigenerational effects	
Maize	Bt (event not mentioned)	Brake et al., 2004. No specific funding mentioned	Mice	8, 16, 26, 32, 63, and 87 days after birth	Testicular development. Litter size. Body weight	2 groups (10 female mice; 6 male mice). 3 male progeny per group sacrificed for each of six time points. 3 generations	No differences in fetal, postnatal, pubertal, or adult testicular development with the GM maize diet	Safe, no multigenerational effects	
Maize	Bt176	Flachowsky et al., 2007. No specific funding mentioned	Broiler chickens, bulls, cows, hens, pigs, quails, sheep	Broiler chickens 35 days (5 weeks),bulls 246 days (35 weeks), cows 246 days (35 weeks approx.), hens 217 days (31 weeks), pigs 91 days (13 weeks), quails 84 days (12 weeks), sheep 91 days (13 weeks)	Digestibility. Feed intake. Health and performance. Meat quality. Reproduction	Broiler chickens: 2 ($n = 17$), in total 34. Bulls: 2 ($n = 20$), in total 40. Cows: 2 ($n = 20$), in total 40. Hens: 2 ($n = 6$), in total 12. Pigs: 2 ($n = 6$), in total 12. Quails: 2 (70 male and 75 female, $n = 145$). Sheep: ($n = 4$). 10 generations for quails; 4 generations for hens	No recombinant DNA found in organs or tissues. No side effects of GM fed to 2nd generation	Safe, no multigenerational effects	
Maize	Bt (event not mentioned)	Kilic and Akay, 2008. No specific funding mentioned	Wistar albino rats	Duration not precised at least 3.5 months (14 weeks)	Histological and biochemical parameters characterizing stomach, duodenum, liver kidney	3 ($n = 9$), in total 27 individuals (18 females, 9 males). 3 generations	No differences in organ weights. Some minor histological changes in liver and kidney	The changes are minor and don't threaten the health of rats but long-term feeding studies with GM crops should be performed on other species	Event not mentioned. Lack of precision regarding duration of the study and the event studied
Maize	Bt176	Trabalza-Marinucci et al., 2008. Italian Ministry of Health	Sheep	44 months (188)	Samples of liver, spleen, pancreas, duodenum, cecal appendix, mesenteric lymph nodes, rumen and abomasum. Immune response, ruminal metabolism, microbial population, meat quality, transgene detection	2 ($n = 53$), in total 106 individuals. 3 generations	Changes in cell nuclei of liver and pancreas	Small effects. In general, GM maize is substantially equivalent to conventional maize but more metabolic research is needed in gastrointestinal organs and the immune response mechanisms	No use of isogenic lines. No evidence provided that the cytosolic differences are reproducible in independant biological replicates nor whether they are observed or not at different time points
Maize	Bt11	Haryu et al., 2009. No specific funding mentioned	Mice	1072 days (153 approx.)	Growth. Gestation, milking periods, reproduction, life span	2 for each generation (31 female mice, 16 male mice), in total 94 individuals. 5 generations	No differences in all parameters.	Safe, no multigenerational effects	
Potato	Phosphinothricin acetyltransferase (*bar* gene)	Rhee et al., 2005. No specific funding mentioned	Rats	5 generations; 70-day intervals before reproduction. 10 weeks	Presence of DNA. Feed consumption. Body weight. Reproductive performance.	Not specified. 5 generations	No difference in all parameters	Safe, no multigenerational effects	No use of isogenic line. Number of animals not mentioned

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Table 3 (*continued*)

Plant	Trait	Reference & Funding	Species	Duration	Parameters	Group (n = number of individuals per group)	Main Findings	Authors' Interpretation of Results	Criticisms
					Development and viability of progeny. Organ weights. Skeletal and visceral deformations. Histopathology				
Soybean	Glyphosate-tolerant soybean (GTS 40-3-2)	Brake and Evenson, 2004. Legislature of the State of South Dakota, Agricultural Experiment Station GMO Grant	Mice	8, 16, 26, 32, and 63 days after birth (from one week approx. to 12 weeks approx.)	Testicular development. Litter size. Body weight	2 groups (10 female mice, 6 male mice), in total 32 individuals. Three male progeny chosen for each of six time points. 3 generations	No differences in fetal, postnatal, pubertal, or adult testicular development with the GM soybean diet	Safe, no multigenerational effects	No use of isogenic line. Uncorrect number of animals
Soybean	Glyphosate-tolerant soybean (GTS 40-3-2)	Daleprane et al., 2009b. State of Rio de Janeiro Research Assistance Foundation and the National Council for Scientific and Technological Development	Wistar rats	Fed throughout life, exact time unclear	Weight gain, protein intake, ration intake. Food Conversion Ratios	3 groups ($n = 8$), in total 24 male mice. 2 generations	Differences between experimental and control		No use of isogenic line. Uncorrect number of animals
Soybean	Glyphosate-tolerant soybean (GTS 40-3-2)	Tudisco et al., 2010. No specific funding mentioned	Goats	60–67 days (8–9 approx.)	DNA in milk and blood	2 groups ($n = 10$) parents, female individuals only; 2 groups ($n = 5$) kids, male individuals only. 2 generations	Presence of transgenic DNA in milk (parents) and blood (parents and offsprings). A significant difference for the level of LDH enzyme, and substitutions between the isoenzymes	Transgenic DNA detection far less important than chloroplastic DNA. LDH modifications suggest a rise of the cell metabolism. No health issue but further studies should be undertaken	No use of isogenic line. Grown in the same conditions not clear. Overinterpretation of the results. Uncorrect number of animals
Triticale	Glufosinate ammonium-tolerant triticale (tolerance to Basta with phosphonithricin as an active substance)	Baranowski et al., 2006. State Committee for Scientific Research	Mice	91 days then mated/killed (at each generation)	Body weight and growth. Presence of transgenic DNA. Blood, kidneys, spleen, liver, thighs.	2 (n = 10 sacrificed at each generation; five females and five males). 5 generations.	No presence of transgenic DNA. No weight differences. No pathological manifestations.	Safe, no multigenerational effects.	
Triticale	Glufosinate ammonium-tolerant wheat (Basta) (and containing the *β-glucuronisdae* gene)	Krzyowska et al., 2010. No specific funding mentioned	Mice	120 days then mated/killed (at each generation)	Immune system	2 ($n = 20$ sacrificed at each generation). Gender not mentioned. 5 generations	In F5 enlarged inguinal and axillary lymph nodes detected. Decrease in T cells in spleen and lymph nodes and decrease in B cells in lymph nodes and blood	B cell compartment in the secondary lymphoid organs expansion not caused by an allergy or a malignant process but further studies should be undertaken	

Table 4
Organs and parameters examined in long term and multigenerational studies.

Organ	Parameters	Plant	Reference
Adrenal	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Brain	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Duodenum	Weight and histopathology	Insect-resistant maize (event not specified)	Kiliç and Akay (2008)
Gills	Na + K + -ATPase activity	Glyphosate-tolerant soybean (event GTS 40-3-2)	Sissener et al. (2009)
Heart	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Heart	Determination of enzymes, detection of chloroplast DNA and transgenic fragment	Glyphosate-tolerant soybean (event GTS 40-3-2)	Tudisco et al. (2010)
Heart (aorta)	Histological analysis	Herbicide-tolerant soybean (event not specified)	Daleprane et al. (2010)
Intestine	Fat content	Insect-resistant maize (event Bt 176); insect-resistant potatoes (containing Cry5-Bt gene); herbicide-tolerant (Pat) maize (event not specified); herbicide-tolerant (Pat) sugar beet; glyphosate-tolerant soybean (GTS 40-3-2)	Flachowsky et al. (2007)
Intestine	Proximal intestine somatic index, mid intestine somatic index, distal intestine somatic index, size	Glyphosate-tolerant soybean (event GTS 40-3-2)	Sissener et al. (2009)
Kidney	Detection of transgenic DNA from plant	Glufosinate ammonium-tolerant triticale (event not specified; tolerance to herbicide with phosphonithricin as an active substance)	Baranowski et al. (2006)
Kidney	Fat content	Insect-resistant maize (event Bt 176); insect-resistant potato (containing Cry5-Bt gene); herbicide-tolerant (Pat) maize (event not specified); herbicide-tolerant (Pat) sugar beet; herbicide-tolerant soybean (GTS 40-3-2)	Flachowsky et al. (2007)
Kidney	Weight and histopathology	Insect-resistant maize (event not specified)	Kiliç and Akay (2008)
Kidney	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Kidney	Head kidney-somatic index, size of head kidney	Glyphosate-tolerant soybean (event GTS 40-3-2)	Sissener et al. (2009)
Kidney	Determination of enzymes, detection of chloroplast DNA and transgenic fragment	Glyphosate-tolerant soybean (event GTS 40-3-2)	Tudisco et al. (2010)
Liver	Histocytochemistry	Glyphosate-tolerant soybean (event GTS 40-3-2)	Malatesta et al. (2002a,b, 2003)
Liver	Enzyme chemistry	Glyphosate-tolerant soybean (event GTS 40-3-2)	Vecchio et al. (2004)
Liver	Detection of transgenic DNA from plant	Glufosinate ammonium-tolerant triticale (event not specified; tolerance to herbicide with phosphonithricin as an active substance)	Baranowski et al. (2006)
Liver	Detection of transgenic DNA	Insect-resistant maize (event Bt 176); insect-resistant potato (containing Cry5-Bt gene); herbicide-tolerant (Pat) maize (event not specified); herbicide-tolerant (Pat) sugar beet; herbicide-tolerant soybean (GTS 40-3-2)	Flachowsky et al. (2007)
Liver	Weight and histopathology	Insect-resistant maize (event not specified)	Kiliç and Akay (2008)
Liver	Protein content, morphology	Glyphosate-tolerant soybean (event GTS 40-3-2)	Malatesta et al. (2008)
Liver	Hepato-somatic index	Glyphosate-tolerant soybean (event GTS 40-3-2)	Sissener et al. (2009)
Liver	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Liver	Determination of enzymes, detection of chloroplast DNA and transgenic fragment	Herbicide-tolerant soybean (event GTS 40-3-2)	Tudisco et al. (2010)
Lung	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Lymphoid	T cell and antibody numbers	Insect-resistant wheat (event not specified)	Krzyzowska et al. (2010)
Muscle	Detection of transgenic DNA from plant	Glufosinate ammonium-tolerant triticale (event not specified; tolerance to herbicide with phosphonithricin as an active substance)	Baranowski et al. (2006)
Muscle	Detection of promoter	Herbicide-resistant soybean (event not specified; containing 5-*enolpyruvylshikimate-3-phosphate* gene)	Suharman et al. (2009)
Ovary	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Ovary	Weight	Insect-resistant maize (event Bt 11 N58-D1)	Haryu et al. (2009)
Pancreas	Histocytochemistry	Glyphosate-tolerant soybean (event GTS 40-3-2)	Malatesta et al. (2002a,b, 2003)
Pancreas	Enzyme chemistry	Glyphosate-tolerant soybean (event GTS 40-3-2)	Vecchio et al. (2004)
Pituitary	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Placenta	Weight	Insect-resistant maize (event Bt 11 N58-D1)	Haryu et al. (2009)
Prostate	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Serum	Enzyme chemistry	Glyphosate-tolerant soybean (event GTS 40-3-2)	Vecchio et al. (2004)
Spleen	Detection of transgenic DNA from plant	Glufosinate ammonium-tolerant triticale (event not specified; tolerance to herbicide with phosphonithricin as an active substance)	Baranowski et al. (2006)
Spleen	Detection of transgenic DNA	Insect-resistant maize (event Bt 176); insect-resistant potatoes (containing Cry5-Bt gene); herbicide-tolerant (Pat) maize (event not specified); herbicide-tolerant (Pat) sugar beet; glyphosate-tolerant soybean (GTS 40-3-2)	Flachowsky et al. (2007)
Spleen	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Spleen	Spleen-somatic index	Glyphosate-tolerant soybean (event GTS 40-3-2)	Sissener et al. (2009)
Spleen	Determination of enzymes, detection of chloroplast DNA and transgenic fragment	Glyphosate-tolerant soybean (event GTS 40-3-2)	Tudisco et al. (2010)
Stomach	Fat content	Insect-resistant maize (event Bt 176); insect-resistant potato (containing Cry5-Bt gene); Herbicide-tolerant (Pat) maize (event not specified); Herbicide-tolerant (Pat) sugar beet; Glyphosate-tolerant soybean (GTS 40-3-2)	Flachowsky et al. (2007)
Stomach	Weight and histopathology	Insect-resistant maize (event not specified)	Kiliç and Akay (2008)
Testis	Histocytochemistry	Glyphosate-tolerant soybean (event GTS 40-3-2)	Malatesta et al. (2002a,b, 2003)
Testis	Cell number, proliferation and differentiation	Insect-resistant maize (event N7070Bt)	Brake et al. (2004)
Testis	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Thymus	Weight and histopathology	Rice containing human T-cell epitope from Japanese cedar pollen allergens	Domon et al. (2009)
Uterus	Weight	Insect-resistant maize (event Bt11 N58-D1)	Haryu et al. (2009)

differences were small and within the range of biological variation. Thus, they concluded this long-term study demonstrated the compositional and nutritional equivalence of Bt-MON810 and its isogenic non-transgenic counterpart.

3.2.2. Herbicide-tolerant soybean

Daleprane et al. (2009a) compared a diet containing glyphosate-tolerant soybean **(event not mentioned)** with organic soybean diet for 455 days (all diets contained 10% protein) in rats ($n = 10$ per group) to investigate impacts on growth and blood composition. Growth rates were comparable for all groups. Biochemical analyses revealed that albumin concentrations and serum protein were similar in all groups except for hematocrit. It should be mentioned that the authors included, as another control, a casein-based diet but none of these results will be discussed here. The same laboratory went onto further study the protein quality of these soybean diets and effects on growth rate, by performing 'multigenerational studies' which are discussed below (Daleprane et al., 2009b). Furthermore, Daleprane et al. (2010) additionally investigated the aorta (thickness of the three layers composing the aorta and total thickness) as well as growth parameters. No differences were observed between GM soybean and non-GM soybean fed groups in any parameter. Taking into account all these results, the authors stated that it "might" be concluded that the transgenic soybean is supposedly nutritionally equivalent to the non-transgenic variety as no nutritional or functional change is observed in rats fed a glyphosate-resistant soybean-based diet. However it is necessary to highlight that no true isogenic line of soybean was used as an appropriate comparator for transgenic soybean; furthermore the non-GM soybean was organically-grown, implying that plant growth conditions were different, but this apparently did not have any effect on all the measured endpoints in animals considered in this study.

Sakamoto et al. (2008) evaluated the safety of GM glyphosate-tolerant soybeans (**event not mentioned**) in male and female rats. The rats were fed a diet containing GM soybeans or non-GM soybeans (from a related strain but it is not stated whether these were isogenic or not) at a concentration of 30% in diet, both being adjusted to an identical nutrient level. These groups were also compared to a group fed a commercial diet (number of individuals per group not given) to evaluate any effect related to a soybean-based diet. Body weight and food consumption were recorded daily. After 104 weeks, at termination, hematology, serum biochemistry, and pathological examinations were made. Several differences in animal growth, food intake, organ weights and histological findings were observed between the rats fed the GM and/or non-GM soybeans. However, body weight and food intake were similar for the rats fed the GM or the non-GM soybeans. Gross necropsy findings, hematological and serum biochemical parameters, and organ weights showed no difference between rats fed the GM or the non-GM soybeans. Thus, there was neither an increase in incidence nor any specific type of non-neoplastic or neoplastic lesions in the GM soybeans group for both sexes. Long-term intake of GM soybeans at an incorporation level of 30% in diet had no apparent adverse effect in rats. In a previous study (which again did not mention the transgenic event), Sakamoto et al. (2007) found similar results in rats at the intermediate examination (26 weeks), and at the termination (52 weeks).

During a two-year study performed only on female mice, Malatesta et al. (2008) compared a diet consisting of 14% glyphosate-tolerant soybean (**event not stated**) and a control diet prepared from a commercial non-GM soybean. The effect of GM soybean on liver in 24-month old female mice was investigated with body weight also measured. In a liver proteome analysis (proteins related to hepatocyte metabolism, stress response, calcium signalling and mitochondria), 49 differences were reported with 39 proteins present at a higher level and 10 at a lower level in GM soybean diet fed mice than in non-GM soybean diet fed ones. These differences are all quantitatively minor and are in the range of differences observed in other studies (see Ricroch et al., 2011) and can be due to genotypic differences or growth conditions of the plant material used (see below). The electron microscopy results showed changes in nuclei shape and alterations in mitochondrial membrane in GM-fed mice, leading the authors to state that these observations are indicative of the induction of some metabolic disruptions. They concluded that GM-soybean affects the ageing of liver both morphologically and functionally and that more investigations are needed. It should be noted that this paper has been severely criticized (Williams and DeSesso, 2010). According to these authors, the study suffers from six methodological errors, namely (i) "*controlling for potential litter effect*", (ii) "*using an appropriate number of experimental animals per group and acquiring a sufficiently robust sample of independent observations*", (iii) "*establishing the representativeness of observations*", (iv) "*adhering to the principles for stereologic morphometry*", (v) "*using appropriate statistical methods (for study design as well as for data analysis)*", (vi) "*controlling for potential confounding factors, including those related to differences in diet phytoestrogen contents*". It should also be noted that none of the papers published by Malatesta and colleagues explicitly state the exact identity of the soybean lines used. It seems likely that the plant material compared in these studies was not isogenic lines but rather GM material and non-GM material that the authors were able to purchase from different commercial sources. In addition, the authors made comments on the possible involvement of herbicide treatment to explain their results, which confirms that the plant material differs by additional parameters other than just the transgene insertion factor and the fact that the plant materials were not grown side by side in the same field. Therefore, these studies do not match the internationally recommended standards for a proper nutritional or toxicological assessment of a GM line. Concerning previous studies (Malatesta et al., 2002a,b, 2003; Vecchio et al., 2004), members of the UK Advisory Committee on Novel Foods and Processes (2006) commented on reports about ultrastructural changes in liver, kidney and testes of mice given diets containing GM soybean, compared with non-GM soybean controls: "*Members noted that the papers did not state the origin of the GM and non-GM soya used in the feeding studies. There were no details of whether the soya had been grown in a field or under controlled conditions and whether or not the GM and non-GM soya were grown, handled and processed under similar conditions. It was also not clear whether the soya used in the control and GM experiments had a similar genetic background. The Committee was unable to determine whether or not the GM and non-GM soya crops had been treated with the herbicide glyphosate, although the authors had suggested that differences in residual levels of glyphosate might be responsible for the observed differences. The Committee also requested data on the nutritional equivalence of the two diets and as well as confirmation on whether or not the same experimental animals were used in each study*".

In a different animal model, salmon, Sissener et al. (2009) observed the effects of feeding a high level of glyphosate-tolerant soybean for 7 months, comparing it to a non-GM soybean control diet (stated to be a near isogenic maternal line). Various parameters were measured to observe the overall effect on health and performance. Measurements were made when fish were in fresh water and then after their transfer into seawater; a total of 4 samplings were taken. The growth rate and weight, on a whole, gave the same results for both groups though the weight of the mid-intestine of non-GM fed fish was heavier throughout the whole study. Among the parameters studied in hematology and plasma clinical biochemistry analyses, only one showed differences between groups: plasma triacylglycerol levels were higher in the

GM-fed fish throughout the whole study. Levels increased from 2.04 mMol on Dec 13th (124 days of diet) to 2.45 mMol on Feb 28th (200 days of diet) in GM fed fish, compared with 1.71 mMol (124 days of diet) to 2.25 mMol (200 days of diet) in non-GM fed fish). Other changes were seen when fish were transferred to seawater but were comparable between diet groups. The authors claim that the changes in triacylglycerol levels could have been due to the variation between the strains of the soybean used as the nutritional composition may vary slightly between the GM and the near isogenic line as no other previous studies in fish show the same findings. They conclude that the observations were not biologically significant and that GM soybean is nutritionally equivalent and as safe as non-GM soybean, thus it can be included in diets.

3.2.3. GM rice seeds containing Japanese cedar pollen allergens

This GM rice produces a hybrid peptide of seven major human T-cell epitopes (7Crp) derived from the *Cry j I and Cry j II* genes from *Cryptomeria japonica* pollen, which encode major human allergens During 26 weeks, cynomolgus macaques were fed with GM rice (Domon et al., 2009). Cv. Kitaake served as a control. The animals were divided into three groups, each comprising three males and three females, and administered a high dose of GM rice, a low dose of GM rice, or a high dose of the parental non-transgenic rice control by oral gavage every day. There were no abnormal clinical signs attributable to administration of GM rice in any group. No adverse effects on behavior or body weight were observed. Serum analysis from animals showed that, with few exceptions, there were no significant differences in hematological or biochemical values between groups. Neither pathological symptoms nor histopathological abnormalities were observed. Repeated oral administration of GM rice has no adverse effects.

3.2.4. What can be learned from long-term studies?

Overall, the available long-term studies do not yield new safety concerns and confirm that the studied GM varieties (most of them are major commercial products) are nutritionally equivalent to their non-GM conventional counterparts. It is particularly important to note that the six publications we examined included a large range of animal models (rat, mouse, cow, and salmon) and various durations of feeding. From these, no biologically-significant differences or adverse health effects were observed. However, in contrast to the maize study, the soybean studies do not state whether isogenic non-GM soybean was used as convenient control. In a number of papers we examined, the event is not even mentioned. Therefore it could be argued that if no non-GM isogenic lines were used (which could well explain some of the reported differences) these studies are not up to the required standards to thoroughly compare and examine the effects induced by GM and non-GM soybean.

When taking into account all the results, no long-term feeding study revealed any deleterious health effects and, therefore, did not provide any supplementary information that would already have been provided by the previously performed 90-day feeding studies (see Table 1).

3.3. Multigenerational studies

The main data from the publications discussed below are listed in Table 3. Within these studies, although rats and mice have sometimes been used, farm animals (dairy cows and bulls, goats, pigs, sheep, hens, broiler chickens, and quails) have mainly been studied.

Parameters measured include body weight, feed intake, detection of DNA from the GM plant in organs, enzyme concentrations or activities, and some reproductive factors. Within these studies, it is important to note that sometimes animals are fed GM-based diets throughout their life, i.e. on a long-term basis, and some are fed only on a short-term (less than 90 days) basis, but all these animals are bred to produce further generations. As shown below, the number of generations varies from 2 to 10. The main goal of these studies was to determine whether GM plants have a detrimental effect on next generations when the present generation was fed GM plants.

3.3.1. Insect-resistant maize

Concerning the general effects of GM plants, such as effects on health, performance and feed intake, on different species, the publication of Flachowsky et al. (2007) is a pivotal one. This review summarizes 18 studies that have been conducted at the Federal Agricultural Research Centre (FAL) in Germany since 1997. The majority (16) of experiments were undertaken using GM feeds based on Bt-maize, Bt-potatoes, glufosinate-tolerant (Pat) maize, glufosinate-tolerant sugar beet, and glyphosate-tolerant soybean. Two other studies were carried out using GM rapeseed which had an altered fatty acids profile (Böhme et al., 2005a), or inulin synthesising potatoes (Böhme et al., 2005b). In all 18 experiments, feeds from the GM lines were compared with their isogenic counterparts. Criteria such as digestibility, feed intake, health, performance, feed quality were studied in cows, bulls, pigs, hens, broiler chicken and quails. The study in hens was conducted for 4 generations and in quails for 10 generations. The other studies (cows, bulls, pigs, broiler chicken) were conducted for 1 generation for a short-term feeding of diet (for a period of 90 days). An additional objective of the study was to look for recombinant DNA in the digestive tract and other animal organs and tissues. No recombinant DNA (between 190 bp and 1000 bp) was found and the results showed that there was no significant difference in the nutritional value of the GM maize and no sign of adverse health effects in animals fed the GM-based diets. For reproductive parameters recorded in quails and hens, no significant difference was found between groups of animals fed diets containing either GM maize, which contains the gene Cry 1A(b)-delta-endotoxin, or non-GM maize.

Trabalza-Marinucci et al. (2008) also conducted a longitudinal study on three generations of sheep fed a Bt176 maize- or non-GM maize-based diet. They evaluated breeding performance, reproductive traits, hematological parameters, antioxidant defenses, lymphocyte proliferative capacity, phagocytosis and intracellular killing of macrophages, and ruminal microbial population and immune response to *Salmonella abortusovis* vaccination for three years. No adverse effect of the GM-based diet was found according to these parameters. No transgenic DNA was detected in tissues, blood or ruminal fluid. However, the authors claimed they observed proliferative activation of basal cells of ruminal epithelium in all GM maize-fed ewes, as well as smaller cell nuclei in hepatocytes and pancreatic acinar cells, which contained increased amounts of heterochromatin and perichromatin granules in GM-fed lambs. They also reported that immune response to *Salmonella* vaccination was more efficient in GM maize-fed sheep advising that it should be necessary to perform new longitudinal studies with a special focus on the effects on the immune system. There are major criticisms to be raised against these results (some of which are termed "preliminary" by the authors themselves). First, it appears that they did not use an isogenic line as a non-GM-comparator and that both lines were not grown under similar conditions. To compensate for these experimental flaws, they measured the composition of the GM and non-GM diets, and they claimed that the compositional differences were "*so minor that they are unlikely to be of any biological significance*". However, this latter comment appears unconvincing. Secondly, there is no evidence provided that the cytosolic differences are reproducible in independent biological replicates or whether they are observed or not at different time points.

Similar criticisms can be raised for the study of Kiliç and Akay (2008). Wistar albino rats were fed a Bt-maize-based diet for three generations, this cultivar being resistant to the corn borer insect. Unfortunately, the exact variety is not specified and the non-transgenic line is not stated as being truly isogenic. Histological and biochemical parameters were studied in liver, kidneys, stomach and duodenum. Even though there was no difference in organ weights, some minor histopathological changes were found in liver and kidney as well as biochemical changes in creatinine, total protein and globulin. These changes were gender-dependent with females exhibiting increased creatinine levels for example. Changes over the three generations were considered as minor, neither statistically significant nor constituting a health hazard. Nonetheless, the authors suggested that long-term studies should be conducted on other species to confirm their results.

The effects of Bt11 maize (N7070Bt) on breeding traits (survival, body weight, feed efficiency, and carcass yield) were evaluated in broiler chickens in a study performed by Brake et al. (2003). No difference was found between the groups fed GM maize or the control diet.

Concerning the effects of GM maize (Bt11 variety 38PO6 and an isogenic line) diet on reproductive performance, Brake and Evenson (2004) studied the testicular development of mice. By studying the germ cell population at six regular periods throughout the life of mice in four successive generations, they determined that the diet induced no detectable effect on testicular development at any stage of life. Similarly, Haryu et al. (2009) carried out work on female mice. By weighing the fetuses, ovaries, placenta, uterus, assessing lifespan and counting the number of fetuses in five generations of mice, therefore studying growth, gestation and reproduction, no significant difference was found between the GM fed and the non-GM fed groups. Apparently these studies (Brake and Evenson, 2004; Haryu et al., 2009) roughly followed the OECD Test Guideline (OECD, 1998) (see Table 3). Twenty animals (10 female and 10 male) were used at each dose level, of which there were three, and a control was used (OECD, 1998; ANSES, 2011).

3.3.2. Herbicide-tolerant soybean

Brake and Evenson (2004) studied the effects of glyphosate-tolerant soybean on the testicular development in three generations of mice with the same methods used with maize as described previously (Brake et al., 2004). No effect of GM soybeans was found on fetal, postnatal, pubertal or adult testicular development.

Daleprane et al. (2009b) studied the use of glyphosate-tolerant soybean and organic soybean (both compared to a control casein diet, which is not discussed here) by measuring the net protein ratio and the protein efficacy ratio on two generations of rats. It should be noted that these parameters are used in nutrition studies, but in this study it is unfortunate that the authors did not adopt conventional parameters such as nitrogen digestibility or apparent or net protein digestibility, and the feed conversion ratio. Some differences were found in body weight ratio, protein intake and quality between the two soybean groups. Some differences between the GM and organic soybean fed groups were found in ration and protein intake, protein intake/weight ratio and calorie intake/weight ratio, and in protein efficacy ratio, net protein ratio and coefficient of alimentary effectiveness of F0 and F1 generations. From one generation to the next, no significant difference in weight was observed within the same group.

Tudisco et al. (2010) studied, in two generations of goats, the effects of glyphosate-tolerant soybean-based feeding and the presence of transgenic DNA fragments in blood and milk during a 15, 30 and 60-day feeding period (60, 30 and 15 days before killing in twenty pregnant dairy goats). The control diet is not precisely characterized ("conventional soybean"). In several organs, the authors found a significant difference in lactic dehydrogenase activity (LDH) and substitutions between the LDH isoenzymes. The LDH activity was measured in liver, heart, kidneys and muscle with an increase in LDH activity observed in liver (LDH1) and kidneys (LDH1), muscle (LDH1 and LDH2), and a decrease in the heart (LDH2 and LDH3) and muscle (LDH5) in kids drinking milk from treated animals. Elevated levels of LDH in tissues could suggest a rise in cell metabolism, but the corresponding enzyme activity in serum remained unchanged, so the effect is not clear and the authors do not consider it as a health issue but state that it should be taken into consideration for future studies. Small plant DNA fragments were detected in milk but also in kids' organs when mothers were fed GM soybean. The detection of transgenic target DNA sequences (35S promoter and CP4 EPSPS) in kids' organs is surprising as these DNA fragments are supposed to originate from the mothers' milk, which contained only low amounts of these DNA fragments. Furthermore, the detection of DNA fragments was not validated by DNA sequencing. In brief, Tudisco et al. (2010) showed some possible effects on metabolism though it is unclear whether this indicates a health risk issue. It is important to note that in this experiment the control group received a diet termed 'conventional' soybean, but it is not clear whether this was isogenic and whether the soybean cultivars were grown in the same conditions.

3.3.3. Herbicide-tolerant potato

In the studies performed by Rhee et al. (2005) in five generations of rats, the *bar* gene, which provides resistance to phosphinothricin, was not found in any of the reproductive organs of the GM-fed male and female rats to which a low level of potato-based diet (5%) was given. Body weight, food consumption, reproductive performance, and organ weight were all examined with no change. The authors conclude that GM potatoes have no effect on multigenerational reproductive and developmental performance.

3.3.4. Herbicide-tolerant triticale

Baranowski et al. (2006) and Krzyzowska et al. (2010) conducted two studies on five generations of mice fed with triticale tolerant to the herbicide glufosinate-ammonium (containing the β-glucuronidase gene (uidA) reporter gene). Baranowski et al. (2006) studied the effects of GM triticale by recording body weight and conducting PCR analysis to detect the presence of transgenic DNA in blood, kidneys, liver, spleen and thigh muscle on five generations. Each generation contained two groups, which were respectively fed either an experimental or a control diet containing 20% (by weight) of conventional triticale grain (except generation F0 that was only fed the control diet) and parameters were measured on mice from the 5 generations (at every generation, mice were sacrificed after 91 days). They also monitored possible pathological effects. They found no weight difference, no presence of transgenic DNA in tissues and no pathological effect.

Krzyzowska et al. (2010) were more concerned with the effects of glufosinate-ammonium tolerant triticale on the immune system. They conducted flow cytometry analysis, histopathological analysis, immunoblot analysis, immunophenotyping and measured the serum levels of cytokines and IgE on mice fed a conventional or a transgenic triticale-based diet containing 20% of the diet for both. These lines are not isogenic but it should be noted that they are the same as the ones used in Baranowski et al. (2006). They found in the fifth generation (only this generation was sacrificed and autopsied) enlarged inguinal and axillary lymph nodes, a decrease in the percentage of T cells in spleen and lymph nodes, increased IL-2 levels (by a factor of 2.5 for the fifth generation compared to controls), and decreased IL-6 levels (by a factor of 0.4 for the fifth generation compared to controls) but no significant changes in the levels of IgE. The authors showed that this expansion of the B cell compartment in the secondary lymphoid organs was not caused by an allergy or a malignant process. Further studies should investigate the reasons of these changes and whether they are reproducible.

3.3.5. What can be learned from multigenerational studies?

Overall, the multigenerational studies on animals fed GM plants do not reveal signs of toxicity or other macroscopic effects on health. Changes in cytological characteristics in some cells and potential differences in metabolism in some organs have been reported (Tudisco et al., 2010), as well as changes in immune responses (Krzyzowska et al., 2010). However, these changes seem to be minor since the authors do not interpret them as potent effects on health. The relevance of the observed differences in some of the parameters is not known and may reflect some natural variation. The authors suggest that additional multigenerational studies should be done in order to study the reproducibility of these results and to try to find the true cause of the detected changes. Unfortunately, it has to be mentioned that, again, these reports suffer from serious weaknesses since they did not use appropriate comparators and this could be the major reason for the changes observed and, hence, the data cannot be interpreted in terms of toxicological effects.

The statistical problem underlying the existence of confounding factors is highlighted in these studies and we also noticed some other recurrent problems in the experimental designs. Some of these issues are poor definition of a control (or group control), weaknesses in the definition of factor levels, lack of a complete combination of factors inside experimental designs, absence of evaluation of the statistical power, and lack of multivariate approaches. Moreover, regulatory agency EFSA (2010) recommended improved methodology for experimental design particularly when statistics are involved.

4. Discussion

General principles outlined in the OECD Test Guideline (1998) or discussed by EFSA (2008) have been built or adjusted to get a robust evaluation for the safety of GM-based diet in a case-by-case basis. These are based on i) the substantial equivalence principle, the use of which is intended to compare chemical composition in macro and micro nutrients and known anti-nutrients and natural toxicants of GM lines and near unmodified isogenic lines, and ii) the toxico-nutritional response of animals fed either a GM-based diet or a control diet in sub-chronic toxicity tests, and if necessary long-term or multigenerational studies.

GM lines with no deliberate metabolic modification are usually found to be nutritionally equivalent to their comparator non-GM line. This is not surprising since these GM lines have been selected, from laboratory and field trials, by comparison with known non-GM lines on various phenotypic traits. Thus, it is highly unlikely that such a comparative process would yield GM lines with major unintended chemical differences. Furthermore, these lines are usually backcrossed to elite lines, which also contribute to their equivalence to these comparator lines. Thus, although this has often been overlooked, the whole process of production of GM commercial lines contributes to the food safety of such lines and no other study has been proven really necessary to assess this safety.

Nevertheless, if doubts about this nutritional equivalence still exist, some experts recommend performing sub-chronic toxicity 90-day tests to assess this uncertainty (Aumaitre, com. pers.). Therefore, in this general step-by-step assessment frame, long-term and multigenerational studies would be performed only after such a sub-chronic toxicity 90-day testing.

4.1. Exploratory studies in the context of a step-by-step approach

In the present review, most of the studies mentioned were not conducted as part of a regulatory safety assessment process but were exploratory studies performed by public research laboratories. Ten out of the 12 long-term studies examined in this review were all performed within the public sector using public funding. Five studies undertaken at the University of Urbino in Italy (Malatesta et al., 2002a,b, 2003), at the Technical University of Munich in Germany (Steinke et al., 2010) and at the Transgenic Crop Research and Development Center in Japan (Domon et al., 2009) did not mention any specific funding. All of the twelve multigenerational studies were performed within the public sector. Eight out of the twelve multigenerational studies did not mention any specific funding (Brake et al., 2003, 2004; Rhee et al., 2005; Flachowsky et al., 2007; Kiliç and Akay, 2008; Haryu et al., 2009; Tudisco et al., 2010; Krzyzowska et al., 2010).

Despite the exploratory nature of the studies reviewed here, the step-by-step approach is supported by their results. Considering all of them, it is clear that GM food is not revealed to be harmful when the duration of feeding is increased to well over 90 days. Therefore, no evidence is available to show that a duration of 90 days is insufficient to assess the effects of GM food. Studies lasting two years, for example, do not seem necessary except when doubt remains after performing 90-day studies. The concept of nutritional equivalence has been proven to be sufficient to assess the safety of GM food and feed, and it has recently been supported by the use of technologies such as metabolomics, proteomics and transcriptomics (see Ricroch et al., 2011 for a review).

Yet, this review reveals deep weaknesses shared by most long-term studies because of non-adherence to standard procedures outlined in the OECD Test (1998).

4.2. Standard protocols and quality of the studies

The studies reviewed here are often linked to an inadequate experimental design that has detrimental effects on statistical analysis as far as the most frequently used statistics are concerned. Internationally agreed test methods should be used for toxicity testing (EFSA, 2011).

The experimental protocol currently used is described in the OECD Test Guideline No. 408, initially designed for assessing the toxicity of chemicals (OECD, 1998). It recommends populations of at least 10 animals per sex and per group, with 3 doses of the test substance and a control group. Six out of the 24 studies examined here used an appropriate number of experimental animals: three long-term studies (Daleprane et al., 2009a, 2010; Sissener et al., 2009) and three multigenerational studies (Brake et al., 2003; Flachowsky et al., 2007; Haryu et al., 2009). It should be mentioned that increasing the number of animals tested increases the statistical power but is more costly. High costs may hinder the public sector from conducting such studies. A balance should be found between robust toxicological interpretations and a reasonable cost (i.e. affordable by the public sector).

Another major problem of the studies examined here is the plant material and its description. Growing GM lines and their comparator side by side can be difficult and even impossible in some countries because of recurrent vandalism or extensive political bans. Furthermore, seventeen out of the twenty-four studies examined did not use isogenic lines for the control diet (or more precisely did not state they used isogenic lines). Comparing two non-isogenic cultivars is problematic when differences are observed since these effects can be caused by the differences between cultivars and not specifically by the transgene. This is simply related to the confounding factor problem and the defective statistical characteristics underlined above, considering the combination of different controlled factors included in the experimental design. That is why some minor histological and biochemical effects that have been found cannot be causally related to the GM plant itself since they could be due to the conditions of the experiment. Nevertheless, inclusion of commercial cultivars may be useful to check whether the observed values fall within the range of observed values for different parameters. However, inclusion of non-isogenic lines/commercial lines cannot replace the recommended complete experimental design built from different controlled independent variables.

One can mention the studies of Daleprane et al. (2009a,b) which, although it is an interesting study, compared a GM diet and a diet containing organic soybean. Not only were both lines not grown side by side but they were also grown using different agricultural practices. Although few differences were observed, an isogenic line grown side by side with the GM line should have been added in the comparative analysis.

In addition, this systematic review and critical examination of the numerous published studies indicate that those which found changes in some parameters did not follow the required standard protocols. One study sorted from our database did not reach the standard requirement of scientific validity for publication (Velimirov et al., 2008) and therefore is not discussed here.

In summary, the major insufficiencies not only include lack of use of near isogenic lines but also statistical power underestimation, absence of repetitions (see below), over-interpretation of differences, which are often within the normal range of variation, and poor toxicological interpretation of the data. As shown in the present review, the over-90 day and multigenerational studies do not reveal any new effect that has not been found in 90-day studies. Thus, it could be assumed that standard protocols are efficient enough to detect adverse effects and there is no need to design new protocols that cannot lead to sound comparisons. Considering that it is a critical issue surrounding GM evaluations that studies of insufficient quality can still be published, it is our opinion that in the future only publications in peer-reviewed journals devoted to toxicology and nutrition should be considered for a critical analysis of scientific evidence related to such topics.

4.3. Cooperation between public laboratories and private firms

Because of recurrent lack of compliance with international standards of many studies, a critical situation has arisen where the private sector may not want to provide plant material for studies. Unfortunately, without such collaboration from the private sector, public laboratories may not always be able to conduct studies using appropriate plants lines. In this context, more rigorous statistical prerequisite and sound toxicological interpretations of the results would encourage a virtuous scientific collaboration between public laboratories and private firms, particularly to access to the different isogenic lines that are true comparator of GM lines.

4.4. Fundamental research and harmonization of protocols

If long-term and multigenerational studies would rarely be used in the regulatory safety assessment of GM whole food and feed as they would constitute the third step to assess the safety, such studies could be used in fundamental research aimed to increase basic knowledge. It would be the case, for example, to check whether these specific types of study may provide supplementary observations not displayed in sub-chronic 90-day studies, or to assess the effects of the chemical composition of a particular diet (for example the effects on metabolism of the amount of maize in diet in addition to the factor GM), or to find out the amount of GM material per diet that is the most suitable to assess the whole food and feed or, more generally, to better design such experiments to proceed to a more convenient assessment of GM-based diets.

However, for generating knowledge of indisputable quality, another improvement in the protocols is necessary, namely reproducibility. As shown in Tables 2 and 3, very few studies for a given plant line have been reproduced using the same animal model. Moreover, studies using the same animal model were performed with different parameters, which lead to the fact that no trials have been carried out twice in the same conditions by different research teams. The most used animal model is mouse, for which only two studies were conducted for maize, two for soybean, two for triticale, and one for potato. Other animal models used in such GM food or feed assessment are rats and cows. Tests conducted according to OECD Test Guideline (1998) and a lot of toxicological studies are carried out on rodents, therefore using rats and mice. Studies on cows are mostly used to study effects on milk composition. With such diversity in models, it is difficult to integrate results in meta-analyses and to interpret these results on a large scale.

The same remarks can be made concerning organs according to Table 4, which shows the variety of organs studied but also the variety of parameters studied by organ. The most studied organ is liver, then kidneys and the digestive tract (stomach and intestine), which are relevant since these organs are primary barriers functionally impacted by nutritional factors or possible toxic events. Indeed, the digestive tract is first exposed to any food toxicant, but also some other organs like liver and kidneys are detoxifying organs. Reproductive organs are also studied to evaluate effects, which may not be harmful for the health but would have an effect on reproductive performance. Further harmonization is needed for the statistical approaches as well as previously quoted parameters, as recently proposed by French Agency with responsibility for food safety, concerning statistical analyses of data from 90-day rat feeding studies (ANSES, 2011).

In addition, such exploratory feeding studies could serve to validate future new studies and their methodologies. For example, high throughput techniques performed in a rigorous statistical framework, could be used to better measure low intensity metabolic disruptions induced by a GM-based feeding. This implies that the use of statistical multivariate analyses can also address the longitudinal follow-up of experimental units. At the same time modeling of other controlled factors such as gender or feeding material from various plant cultivars can be pursued in addition to the GM factor *stricto sensu*. These techniques would help to shed light on the inherent metabolic plasticity of the animal model, which could be impacted by variation of diet because of the GM material, the cultivar or other controlled independent variables. Recently, sensitivity of this approach to detect minor but statistically significant homeostatic transitions in metabolically disrupted models has been well demonstrated in nutritional or sub-toxicological studies (Fardet et al., 2007; Domange et al., 2008).

Such basic research would help to establish a clearer view (i.e. with no conflicting advice) on how to combine or harmonize various experimental designs, namely standardized regulatory-oriented experimental designs consisting of either short-term (21–28 days), middle term (91–105 days) or long-term (180–720 days) protocols, or multigenerational studies. They would help to better document all the factors involved in the calculation of the variance (cultivar, event, individual variability in a longitudinal follow-up of the animal model, phenotypic variability of plant and year effect, etc.) and to prioritize the importance of these factors.

5. Conclusion

Long-term and multigenerational studies have been used as part of exploratory fundamental research projects. Up to now, none of them have provided supplementary information indicating that 90-day rodent feeding studies defined by the Guideline No. 408 (OECD, 1998) would not be sufficient to serve as a sound experimental basis for regulatory assessment of new GM traits. Indeed, only the 90-day rodent feeding studies are recommended in some specific cases to detect any hazard as discussed previously (EFSA, 2008). Therefore, long-term and multigenerational studies should only be conducted in a case-by-case approach for GM food safety regulatory assessment if some reasonable doubt remains after a 90-day feeding trial.

The observations of major flaws in some papers highlight the urgent need to improve the reviewing process before publication of papers addressing this subject. This would avoid spreading confusion in the general press, which may not be able to judge the real scientific quality of publications.

Complementary fundamental research should be conducted using different animal models, but a need for harmonization between studies is crucial to provide better results that are more reproducible within a given animal model and more comparable between neighboring animal models. Such research would help to better analyze the physiological differences arising between short, mid and long-term tests and, hence, the conditions of choice of the most appropriate experimental design.

Conflict of Interest

The authors declare that there are no conflicts of interests.

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Prevalence and impacts of genetically engineered feedstuffs on livestock populations[1]

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ABSTRACT: Globally, food-producing animals consume 70 to 90% of genetically engineered (GE) crop biomass. This review briefly summarizes the scientific literature on performance and health of animals consuming feed containing GE ingredients and composition of products derived from them. It also discusses the field experience of feeding GE feed sources to commercial livestock populations and summarizes the suppliers of GE and non-GE animal feed in global trade. Numerous experimental studies have consistently revealed that the performance and health of GE-fed animals are comparable with those fed isogenic non-GE crop lines. United States animal agriculture produces over 9 billion food-producing animals annually, and more than 95% of these animals consume feed containing GE ingredients. Data on livestock productivity and health were collated from publicly available sources from 1983, before the introduction of GE crops in 1996, and subsequently through 2011, a period with high levels of predominately GE animal feed. These field data sets, representing over 100 billion animals following the introduction of GE crops, did not reveal unfavorable or perturbed trends in livestock health and productivity. No study has revealed any differences in the nutritional profile of animal products derived from GE-fed animals. Because DNA and protein are normal components of the diet that are digested, there are no detectable or reliably quantifiable traces of GE components in milk, meat, and eggs following consumption of GE feed. Globally, countries that are cultivating GE corn and soy are the major livestock feed exporters. Asynchronous regulatory approvals (i.e., cultivation approvals of GE varieties in exporting countries occurring before food and feed approvals in importing countries) have resulted in trade disruptions. This is likely to be increasingly problematic in the future as there are a large number of "second generation" GE crops with altered output traits for improved livestock feed in the developmental and regulatory pipelines. Additionally, advanced techniques to affect targeted genome modifications are emerging, and it is not clear whether these will be encompassed by the current GE process-based trigger for regulatory oversight. There is a pressing need for international harmonization of both regulatory frameworks for GE crops and governance of advanced breeding techniques to prevent widespread disruptions in international trade of livestock feedstuffs in the future.

Key words: genetic engineering, genetically modified organisms, livestock feed, safety

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INTRODUCTION

The first genetically engineered (**GE**) feed crops were introduced in 1996. Their subsequent adoption has been swift. In 2013, GE varieties were planted on more than 95% of sugar beet, 93% of soy, and 90% of all cotton and corn acres in the United States (USDA National Agricultural Statistics Service, 2013). Global livestock populations constitute the largest consumers of GE feed crops. Independent studies have shown the compositional equivalence of the current generation of GE crops (Cheng et al., 2008; Garcia-Villalba et al., 2008; Herman and Price, 2013; Hollingworth et al., 2003), and no significant differences in feed digestibility, performance, or health have been observed in livestock that consume GE feed (Flachowsky et al., 2012). Similarly, it is not possible to detect differences in nutritional profiles of animal products after consumption of GE feed (Guertler et al., 2010; Tufarelli and Laudadio, 2013).

Despite these findings, some states have considered legislation that would require mandatory GE labeling

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of meat, milk, and eggs derived from animals that have eaten GE feed (CAST, 2014). Furthermore, some food companies are actively targeted by campaigns to promote products from animals that are fed non-GE diets. Given the widespread adoption of GE crops, the segment of animal agriculture that is currently feeding non-GE diets is relatively small. Approximately 0.8% of U.S. cropland and 0.5% of U.S. pasture were certified organic in 2011 (USDA National Agricultural Statistics Service, 2012), and only a portion of organic crops are used for animal feed.

Our objective was to briefly review the literature on livestock GE feeding studies and the composition of animal products derived from animals fed a GE diet. We gave special attention to health studies of animals, including an analysis of publicly available data on the health of commercial livestock populations since the introduction of GE crops in 1996. Also, we summarized the global usage and trade of GE feedstuffs along with the estimated size of GE-sensitive markets. Finally, we discussed issues regarding pipeline and regulation of GE crops with modified output traits, asynchronous regulatory approvals, and novel breeding technologies.

Livestock Feeding Studies with Genetically Engineered Feed

A total of 165 GE crop events in 19 plant species, including those used extensively in animal feed (alfalfa, canola, corn, cotton, soybean, and sugar beet), have been approved in the United States (James, 2013). Before approval, each new GE crop goes through a comprehensive risk assessment. The risk analysis of GE organisms is governed by internationally accepted guidelines developed by the Codex Alimentarius Commission (www.codexalimentarius.org). One leading principle is the concept of substantial equivalence, which stipulates that any new GE variety should be assessed for its safety by comparing it with an equivalent, conventionally bred variety that has an established history of safe use. Over the past 20 yr, the U.S. Food and Drug Administration found all of the 148 GE transformation events that they evaluated to be substantially equivalent to their conventional counterparts, as have Japanese regulators for 189 submissions (Herman and Price, 2013). By contrast, plant varieties developed through other processes of achieving genetic changes (e.g., radiation mutagenesis) go through no formal risk assessment before being placed on the market. There have been instances where plants bred using classical techniques have been unsuitable for human consumption. For example, the poison α-solanine, a glycoalkaloid, was unintentionally increased to unacceptable levels in certain varieties of potato through plant breeding resulting in certain cultivars being withdrawn from the U.S. and Swedish markets due to frequently exceeding the upper safe limit for total glycoalkaloid content (Petersson et al., 2013).

The difficulties associated with the safety and nutritional testing of whole foods/feed derived from GE crops, which contain thousands of bioactive substances, are well known (reviewed in Bartholomaeus et al., 2013). These include the fact that the quantity of the GE food that can be included in the diet of test animals is limited by the potential to generate nutritional imbalances and might not be high enough to detect adverse effects. Substantial differences in composition could be present without producing a recognizably meaningful difference between treatment groups fed whole foods. Many toxicologists concur that animal feeding trials of whole GE food have a low power to detect adverse effects and contribute little, if anything, to the safety assessment of whole foods (Kuiper et al., 2013). Far more sensitive analytical, bioinformatical, and specific toxicological methods exist to identify unintended effects resulting from plant breeding and provide more precise and quantifiable data for the safety evaluation of whole foods.

In 2013, the European Union (**EU**) Standing Committee on the Food Chain and Animal Health (Brussels, Belgium) adopted a regulation mandating a 90-d subchronic rodent feeding study (OECD, 1998) for every single GE transformation event. This is despite the fact that the European Food Safety Authority (2008; Parma, Italy) states that such testing is only warranted when driven by a specific hypothesis indicated by molecular, compositional, phenotypic, agronomic, or other analysis (e.g., metabolic pathway considerations) of the particular GE event. This mandate is seen by some as interference in the risk assessment of GE foods based on pseudoscience or political considerations (Kuiper et al., 2013). The United States and Australia/New Zealand explicitly do not require a 90-d subchronic rodent feeding study or actively discourage their conduct due to their negligible scientific value.

Studies in which GE crops are fed to target (food-producing) animals have focused less on GE risk assessment and more on evaluating the nutritional properties of the GE crop as well as resulting animal performance and health as compared to the results when fed an isogenic counterpart. Clear guidelines on experimental design for these types of studies have been developed (International Life Sciences Institute, 2003, 2007).

Multiple generations of food animals have been consuming 70 to 90% of harvested GE biomass (Flachowsky et al., 2012) for more than 15 yr. Several recent comprehensive reviews from various authors summarize the results of food-producing animal feeding studies with the current generation of GE crops (Deb et al., 2013; Flachowsky, 2013; Flachowsky et al., 2012; Tufarelli and Laudadio, 2013; Van Eenennaam, 2013). Studies have been conducted with a variety of food-producing animals including sheep, goats, pigs, chickens, quail, cattle, water buffalo, rabbits, and fish fed different GE crop varieties. The results have consistently revealed that the performance and health of GE-fed animals were comparable with those fed near-isogenic non-GE lines and commercial varieties. Many authors came to the same conclusion a decade ago (Aumaitre et al., 2002; Faust, 2002), suggesting that little contradictory data has emerged over the past 10 yr, despite the increased global prevalence of GE feed.

A number of long-term (of more than 90 d and up to 2 yr in duration) feeding trials and multigenerational studies conducted by public research laboratories using various animal models including pigs, cows, quail, and fish have also been reviewed (Ricroch, 2013; Ricroch et al., 2013; Snell et al., 2012). Significant among these studies are 2 thorough multigenerational studies that examined the long-term effects of feeding a GE corn variety (MON810, expressing the insecticidal Cry1Ab protein from *Bacillus thuringiensis* [**Bt**], one of the few GE corn varieties approved for cultivation in the EU) to food-producing animals, specifically, a German study in dairy cattle and an Irish study in pigs (Guertler et al., 2010, 2012; Steinke et al., 2010; Walsh et al., 2011, 2012 a, b, 2013; Buzoianu et al., 2012 a, b, c, d, 2013 a, b). The results from the multiple papers resulting from these 2 studies are summarized in Table 1. These studies were notable in that they included appropriate controls consuming isogenic non-GE lines of corn, and both comprehensively examined a range of phenotypes and indicators of growth and health and also used sophisticated techniques to look for the presence of recombinant DNA (**rDNA**) and Bt protein in the tissues and products derived from these GE-fed animals.

Results from these comprehensive studies revealed the compositional and nutritional noninferiority of GE corn to its isogenic control and an absence of long-term adverse effects from GE corn consumption. Organ pathology and function were similar between animals fed GE and non-GE corn, and there were no adverse effects of feeding GE corn on small intestinal morphology or the gut microbiota. Antibodies specific to the GE corn protein (Cry1Ab) were not detected in the blood, indicating the absence of an allergic-type immune response to the protein. Neither the *cry1Ab* gene nor the Cry1Ab protein was found in the blood, organs, or products of animals fed GE corn, indicating that neither the intact rDNA nor the intact recombinant protein migrated from the digestive system of the animal into other body tissues or edible animal products.

Even though these 2 comprehensive studies overwhelmingly revealed that a diet of Bt corn was not associated with long-term deleterious effects on the immune systems or animal performance, there were statistically significant differences in some of the parameters measured. Although the authors concluded that these differences were not of biological relevance, significant findings in any parameter in animal feeding studies have been interpreted by some as evidence of harm (Dona and Arvanitoyannis, 2009). Others have pointedly responded that statistical differences per se are not "adverse effects" and need to be considered in terms of their biological importance (Rickard, 2009). The European Food Safety Authority clarified the difference between statistical significance and biological relevance (European Food Safety Authority, 2011). In the absence of some predefined understanding of what changes might be of biological relevance, studies risk becoming "hypothesis-less fishing trips." Post hoc analysis of a large number of variables in a data set with a small sample size can lead to spurious conclusions because such studies "are fraught with differences that are not biologically significant between groups from simple variation and probability" (DeFrancesco, 2013).

The Federation of Animal Science Societies maintains an extensive bibliography of food-producing animal GE feeding studies (FASS 2014). Given the large number of 90-d subchronic rodent and food-producing animal GE feeding studies that currently exist in the literature, it is worth questioning the value of more animal feeding studies as part of a GE risk assessment for crops that are substantially equivalent to conventional comparators (Flachowsky, 2013). The rationale for conducting long-term feeding trials and multigenerational studies need to be explicitly stated, especially given that GE proteins are digested in the gut and no intact GE protein has been found in the bloodstream. Once compositional equivalence has been established for a GE crop, animal feeding studies add little to the safety assessment (Bartholomaeus et al., 2013).

There are less than 100 long-term (>90 d) and multigenerational target animal GE feeding studies in the peer-reviewed literature, which has prompted some to call for more of these types of feeding studies (DeFrancesco, 2013). Although such studies may seem intuitively appealing, they must result in novel useful data to justify the additional time, expense, and animal experimentation. Objective analyses of available data indicate that, for a wide range of substances, reproductive and developmental effects observed in long-term studies are not potentially more sensitive endpoints than those examined in 90-d rodent subchronic toxicity tests (European Food Safety Authority, 2008). There is no evidence that long-term and multigenerational feeding studies of the first generation of GE crops that have been conducted to date have uncovered adverse effects that were undetected by short-term rodent feeding studies (Snell et al., 2012). In the context of GE feed risk assessment, they argue that the decision to conduct long-term and

Table 1. Summary results of 2 comprehensive evaluations of target animal effects of long-term feeding of genetically engineered feed (Bt-MON810 corn) to dairy cattle and pigs[1]. Table adapted from Ricroch et al. (2013)

Study Design	Methods	Results	Conclusions	Reference
A. Dairy cattle study				
36 Simmental dairy cows (9 primiparous and 9 multiparous per treatment group) were assigned to 2 feeding groups and fed with diets based on whole-crop silage, kernels, and whole-crop cobs from GE corn (Bt-MON810) or its isogenic non-GE counterpart as main components. The 765-d study included 2 consecutive lactations.	Feed intake, milk production and composition, and body condition over 25 mo	There were no consistent effects of feeding GE corn or its isogenic control on milk composition or body condition. All changes fell within normal ranges.	Compositional and nutritional equivalence of GE corn to its isogenic control. No long-term effects.	Steinke et al. (2010)
	Gene expression pattern of markers for apoptosis, inflammation, and cell cycle from gastrointestinal tract and samples from liver	Statistical analysis of the examined gene expression pattern revealed no significant difference in the gene expression profile of cows fed transgenic or near-isogenic feed ration	Genetically engineered maize MON810 does not have any effect on major genes involved in apoptosis, inflammation, and cell cycle in the gastrointestinal tract and in the liver of dairy cows.	Guertler et al. (2012)
	Fate of *cry1Ab* DNA and recombinant protein	All blood, milk, and urine samples were free of recombinant DNA and protein. The *cry1Ab* gene was not detected in any fecal samples; however, fragments of the Cry1Ab protein were detected in feces from all cows fed transgenic feed.	Milk of dairy cows fed GE corn for 25 mo should be classified not different from milk of cows fed non-GE corn.	Guertler et al. (2010)
B. Pig study				
Large white × landrace cross-bred male 40-d-old pigs (n = 40) were fed 1 of the following treatments: 1) isogenic corn-based diet for 110 d (isogenic), 2) Bt corn-based diet (MON810) for 110 d (Bt), 3) isogenic corn-based diet for 30 d followed by Bt corn-based diet for 80 d (isogenic/Bt), and 4) Bt corn-based diet (MON810) for 30 d followed by isogenic corn-based diet for 80 d (Bt/isogenic).	Feed intake, growth, characteristics, and body composition. Heart, kidneys, spleen and liver weight and histological analysis. Blood and urine analysis.	No difference in overall growth, body composition, organ weight, histology and serum and urine biochemistry. A significant treatment × time interaction was observed for serum urea, creatinine, and aspartate aminotransferase.	Serum biochemical parameters did not indicate organ dysfunction; changes were not accompanied by histological lesions. Long-term feeding of GE maize did not adversely affect growth or the selected health indicators investigated.	Buzoianu et al. (2012a)
	Effect on intestinal microbiota	Counts of the culturable bacteria enumerated in the feces, ileum, or cecum were not affected by GE feed. Neither did it influence the composition of the cecal microbiota, with the exception of a minor increase in the genus *Holdemania*.	Feeding Bt corn to pigs in the context of its influence on the porcine intestinal microbiota is safe.	Buzoianu et al. (2012d)
	Hematological analysis, measurement of cytokine and Cry1Ab-specific antibody production, immune cell phenotyping, and *cry1Ab* gene and truncated Bt toxin detection	On d 100, lymphocyte counts were higher ($P < 0.05$) in pigs fed Bt/isogenic than pigs fed Bt or isogenic. Erythrocyte counts on d 100 were lower in pigs fed Bt or isogenic/Bt than pigs fed Bt/isogenic ($P < 0.05$). Neither the truncated Bt toxin nor the *cry1Ab* gene was detected in the organs or blood of pigs fed Bt corn.	Perturbations in peripheral immune response were thought not to be age specific and were not indicative of Th 2 type allergenic or Th 1 type inflammatory responses. No evidence of *cry1Ab* gene or Bt toxin translocation to organs or blood following long-term feeding.	Walsh et al. (2012b)
Large White × Landrace cross-bred male pigs (9 per treatment group) fed diet containing 38.9% GE or non-GE isogenic parent line corn for 31 d.	Growth performance, intestinal histology, and organ weight and function.	Short-term feeding of Bt MON810 corn to weaned pigs resulted in increased feed consumption, less efficient conversion of feed to gain, and a decrease in goblet cells/mum of duodenal villus. There was a tendency for an increase in kidney weight, but this was not associated with changes in histopathology or blood biochemistry.	The biological significance of these findings is currently being clarified in long-term exposure studies in pigs.	Walsh et al (2012a)
	Effects on the porcine intestinal microbiota were assessed through culture-dependent and -independent approaches.	Fecal, cecal, and ileal counts of total anaerobes, Enterobacteriaceae, and Lactobacillus were not significantly different between pigs fed the isogenic or Bt corn-based diets. Furthermore, high-throughput 16S rRNA gene sequencing revealed few differences in the compositions of the cecal microbiotas.	*Bacillus thuringiensis* corn is well tolerated by the porcine intestinal microbiota.	Buzoianu et al. (2012c)
	Immune responses and growth in weanling pigs. Determined the fate of the transgenic DNA and protein in vivo.	Interleukin-12 and interferon gamma production from mitogenic stimulated peripheral blood mononuclear cells decreased in GE-fed pigs. Cry1Ab-specific IgG and IgA were not detected in the plasma of GE corn-fed pigs. The detection of the *cry1Ab* gene and protein was limited to the gastrointestinal digesta and was not found in the kidneys, liver, spleen, muscle, heart, or blood.	No evidence of *cry1Ab* gene or protein translocation to the organs and blood of weaning pigs. The growth of pigs was not affected by feeding GE corn. Alterations in immune responses were detected; however, their biologic relevance is questionable.	Walsh et al. (2011)

continued

Table 1. (cont.)

Large White × Landrace cross-bred female pigs (12) – Fed for approximately 143 d throughout gestation and lactation $F_0 + 1$ generation (offspring at birth).	Hematological and immune functions to detect possible inflammatory and allergenic responses at various times. Attempts to detect Cry1Ab protein in blood and feces at various times.	Cytokine production similar between treatments. Some differences in monocyte, granulocyte, or lymphocyte subpopulations counts at some times, but no significant patterns of changes.	No indication for inflammation or allergy due to GE corn feeding. Transgenic material or Cry1Ab-specific antibodies were not detected in sows or offspring.	Buzoianu et al. (2012b)
Large White × Landrace cross-bred pigs (10) – Corn dietary inclusion rate identical between treatments (isogenic parent line corn from service to weaning and GE corn from service to weaning [Bt]) and ranged from 86.6% during gestation to 74.4% during lactation). Offspring (72) fed in 4 dietary treatments as follows: 1) non-GE corn-fed sow/ non-GE corn-fed offspring (non-GE/non-GE), 2) non-GE corn-fed sow/GE corn-fed offspring (non-GE/GE), 3) GE corn-fed sow/non-GE corn-fed offspring (GE/non-GE), and 4) GE corn-fed sow/GE corn-fed offspring (GE/GE) for 115 d.	Pig growth performance, BW, and feed disappearance recorded at the time of each dietary change (at weaning [d 0] and on d 30, 70, and 100) and at harvest (d 115). At harvest, organ weight, histological observations, and cold carcass weight. Serum biochemistry.	No pathology observed in the organs. Offspring of sows fed Bt corn had improved growth throughout their productive life compared to offspring of sows fed non-GE corn, regardless of the corn line fed between weaning and harvest. Some minor differences in average daily gain, carcass and spleen weights, dressing percentage, and duodenal crypt depths for offspring from GE fed or in average daily feed intake for offspring from sows fed GE and for GE-fed pigs or in liver weight for pigs in the GE/GE.	Feeding GE Bt corn from 12 d after weaning to slaughter had no adverse effect on pig growth performance, body composition, organ weights, carcass characteristics, or intestinal morphology. Transgenerational consumption of GE corn diets not detrimental to pig growth and health.	Buzoianu et al. (2013a)
	Sequence based analysis of the intestinal microbiota of sows and their offspring fed GE corn	At d 115 postweaning, GE/non-GE offspring had lower ileal Enterobacteriaceae counts than non-GE/non-GE or GE/GE offspring and lower ileal total anaerobes than pigs on the other treatments. Genetically engineered corn-fed offspring also had higher ileal total anaerobe counts than non-GE corn-fed offspring, and cecal total anaerobes were lower in non-GE/GE and GE/non-GE offspring than in those from the non-GE/non-GE treatment. The only differences observed for major bacterial phyla using 16S rRNA gene sequencing were that fecal Proteobacteria were less abundant in GE corn-fed sows before farrowing and in offspring at weaning, with fecal Firmicutes more abundant in offspring.	While other differences occurred, they were not observed consistently in offspring, were mostly encountered for low-abundance, low-frequency bacterial taxa, and were not associated with pathology. Therefore, their biological relevance is questionable. This confirms the lack of adverse effects of GE corn on the intestinal microbiota of pigs, even following transgenerational consumption.	Buzoianu et al. (2013b)
	The effects of feeding GE corn during first gestation and lactation on maternal and offspring health serum total protein, creatinine and gamma-glutamyltransferase activity, serum urea, platelet count, and mean cell Hb concentration	Genetically engineered corn-fed sows were heavier on d 56 of gestation. Offspring from sows fed GE corn tended to be lighter at weaning. Sows fed GE corn tended to have decreased serum total protein and increased serum creatinine and gamma-glutamyltransferase activity on d 28 of lactation. Serum urea tended to be decreased on d 110 of gestation in GE corn-fed sows and in offspring at birth. Both platelet count and mean cell Hb concentration (MCHC) were decreased on d 110 of gestation in GE corn-fed sows; however, MCHC tended to be increased in offspring at birth.	There was a minimal effect of feeding GE corn to sows during gestation and lactation on maternal and offspring serum biochemistry and hematology at birth or BW at weaning.	Walsh et al. (2013)

[1]GE = genetically engineered; Bt = *Bacillus thuringiensis*; Hb = hemoglobin.

multigenerational studies should be reserved for cases where some reasonable doubt remains following a 90-d feeding trial triggered by a potential hazard identified in the compositional analysis of the GE crop or other available nutritional or toxicological data.

Field Datasets of Livestock Populations Fed with Genetically Engineered Feed

Although a small number of controlled long-term and multigenerational feeding trials of commercialized GE crops in food-producing species are available in the peer-reviewed literature, large numbers of livestock in many countries have been consuming GE feed for over 15 yr. Hence, a very large and powerful set of GE-fed target animal data has been quietly amassing in public databases. United States agriculture feeds billions of food-producing animals each year, with annual broiler numbers alone exceeding the current size of the global human population (Table 2). During 2011, less than 5% of U.S. animals within each of the major livestock sectors were raised for certified National Organic Program (**NOP**) markets that specifically prohibit the feeding of GE feed (Table 2). Given the increase in GE adoption rates between 2000 and 2013, it can be predicted that the vast majority of conventionally raised livestock in

Table 2. Organic livestock production statistics in the United States (2011)

Industry	Number of organic farms in the United States[1]	Number of animals on organic farms[1]	Total number of livestock animals in the United States[2]	Organic livestock numbers as percent of the U.S. total[3]
Broilers	153	28,644,354	8,607,600,000	0.33%
Layers	413	6,663,278	338,428,000	1.97%
Turkeys	70	504,315	248,500,000	0.20%
Beef cows	488	106,181	30,850,000	0.34%
Dairy cows	1,848	254,711	9,150,000	2.78%
Hogs	97	12,373	110,860,000	0.01%

[1] USDA National Agricultural Statistics Service, 2012.

[2] USDA Economics, Statistics, and Market Information System, 2013.

[3] USDA Economic Research Service, 2013.

the United States consumed feed derived from GE crops over the past decade. Cumulatively, this amounts to over 100 billion animals consuming some level of GE feed between 2000 and 2011 (Table 3).

The duration and level of exposure to GE feed would be expected to vary depending on the animal industry. For example, in a typical U.S. broiler operation, chickens are fed for 42–49 d on diets that are composed of approximately 35% soybean meal and 65% corn grain, whereas in others species, longer-term exposure would be the norm (e.g., dairy cows over recurrent lactations). The average U.S. dairy cow has a productive life of 5 yr with 3 conceptions, 3 gestations, and 3 lactations. A typical U.S. dairy diet contains 50% corn silage, 20% corn grain, and 10% dehulled soybean meal. Also, many cows receive large portions of their rations as ground corn grain, fuzzy cottonseed (no processing except for removal of the lint), or roasted full-fat soybeans. Other GE sources of animal feed include alfalfa hay, sugar beet pulp, corn distillers grains or other coproducts from corn processing, cottonseed meal, canola meal, and soy hulls. A beef cow on the range might consume only some GE alfalfa hay, but her progeny entering the feedlot might be expected to consume a ration containing high quantities of GE feed during their 120 d in the feedlot before harvest. Depending on the feeding stage and relative feed prices, feedlot rations will consist of about 80 to 85% grain (usually corn); distillers' grains and/or other sources of starch/energy; and 10 to 15% hay, silage, or other forage. The remaining share of the ration will include some protein source such as soybean or cottonseed meal (Mathews and Johnson, 2013), also likely to be of GE origin.

Table 3. Estimated cumulative number of livestock raised in the United States during the period from 2000 to 2011

Industry[1]	United States
Broilers	94,683,600,000
Layer Hens	3,722,708,000
Turkeys	2,733,500,000
Beef cattle	339,350,000
Dairy Cows	33,550,000
Hogs	1,219,460,000
Total	102,732,168,000

[1] Numbers for broilers, hogs (barrows and gilts), and beef cattle (steers) are for slaughtered animals during calendar year. Dairy animals are number of dairy cows in a calendar year divided by 3 to account for 3 lactations per animal.

It would be reasonable to hypothesize that if animal feed derived from GE crops had deleterious effects on animals consuming GE feed, then animal performance and health attributes in these large commercial livestock populations would have been negatively impacted. To examine this hypothesis further, in October 2013, data on livestock health were collated from publicly available sources in the United States from before the introduction of GE crops in 1996 through 2000 through 2011, a decade when high levels of GE ingredients would be expected to be present in livestock feed based on the known extent of GE crop cultivation. Data were collected for the broiler, dairy, hog, and beef industries. In general, USDA data sets were from the Economics, Statistics, and Market Information System (2013). Additional data for broilers were available from the National Chicken Council (2011) and were 1) days to market, 2) feed efficiency (feed to meat gain ratio), and 3) percent mortality.

Yearly data on cattle condemnation rates were available for 1999 through 2002 from the USDA Food Safety and Inspection Service (**FSIS**) website (USDA Food Safety and Inspection Service, 2003) and from 2003 through 2007 based on a Freedom of Information Act request as reported (White and Moore, 2009). Data from 1994 was collected from the National Non-Fed Beef Quality Audit as reported (Boleman et al., 1998). Non-fed beef is from culled cows and bulls (i.e., animals that do not spend a significant amount of time being "fed" in a feedlot). Data were analyzed to compare trends before and after the introduction of GE feed into livestock diets. Regression analyses were performed for the period 1983 through 1994 as representative of a period with no GE feed and for the period from 2000 through 2011 as a period with high levels of GE feed based on high rates of GE crop adoption. Where data were available for both time periods, the slope of the regression lines between periods was compared using an unpaired *t* test.

Table 4. Livestock production statistics in the United States before and after the introduction of genetically engineered feed in 1996

Year	Milk yield, kg	Somatic cell count, cells/mL, 1,000s	Carcass wt, kg, broiler	Carcass wt, kg, hog	Carcass wt, kg, cattle	Condemned, %	Broiler			Cattle postmortem condemned, %			
										Fed cattle		Non-fed cattle	
							Market age, d	Feed to gain	Mortality rate, %	Steers	Heifers	Cows	Bulls
1983	5,708		1.82	75.3	318.8	1.54							
1984	5,667		1.85	75.7	317.5	1.60							
1985	5,910		1.87	76.6	329.3	1.74	49	5	2				
1986	6,029		1.89	77.1	327.4	1.90							
1987	6,252		1.91	77.6	325.2	1.91							
1988	6,446		1.92	78.5	330.2	1.95							
1989	6,460		1.93	78.0	336.1	1.95							
1990	6,640		1.95	79.4	336.1	1.83	48	5	2				
1991	6,742		1.97	79.8	343.3	1.87							
1992	6,995		2.01	79.8	344.7	1.72							
1993	7,054		2.03	81.2	338.8	1.58							
1994	7,315		2.06	81.6	351.9	1.68						2.6	
1995	7,461	304	2.08	82.1	348.8	1.79	47	5	1.95				
1996	7,485	308	2.12	82.1	347.4	1.80							
1997	7,671	314	2.14	83.9	346.5	1.82							
1998	7,797	318	2.16	83.9	357.8	1.86				0.09	0.10	2.22	0.26
1999	8,059	311	2.22	84.8	359.6	1.74				0.11	0.20	2.11	0.31
2000	8,256	316	2.22	86.6	361.9	1.56	47	5	1.95	0.13	0.17	2.71	0.32
2001	8,226	322	2.24	87.5	361.9	1.31				0.09	0.10	2.67	0.31
2002	8,422	320	2.28	87.5	373.2	1.07				0.08	0.09	2.77	0.24
2003	8,503	319	2.31	88.0	359.2	1.00				0.09	0.08	2.92	0.75
2004	8,597	295	2.34	88.0	361.0	1.13				0.08	0.08	2.44	0.35
2005	8,878	296	2.39	89.3	370.5	1.04	48	4	1.95	0.07	0.07	2.59	0.30
2006	9,048	288	2.44	89.8	377.8	1.22	48	5	1.96	0.06	0.07	2.34	0.30
2007	9,191	276	2.45	89.8	376.4	1.16	48	4.5	1.95	0.05	0.06	2.21	0.28
2008	9,250	262	2.48	89.8	380.0	1.10	48	4.5	1.93				
2009	9,332	233	2.48	90.7	384.1	0.91	47	4.1	1.92				
2010	9,591	228	2.53	91.2	378.7	0.88	47	4.0	1.92				
2011	9,680	217	2.58	92.1	381.4	0.87	47	3.8	1.91				

Livestock production statistics for the United States before and after the introduction of GE feed crops in 1986 are summarized in Table 4. In all industries, there were no obvious perturbations in production parameters over time. The available health parameters, somatic cell count (an indicator of mastitis and inflammation in the udder) in the dairy data set (Fig. 1), postmortem condemnation rates in cattle (Fig. 1), and postmortem condemnation rates and mortality in the poultry industry (Fig. 2) all decreased (i.e., improved) over time.

All animals arriving at USDA-inspected slaughter facilities undergo both antemortem and postmortem inspections to identify abnormalities. Carcasses are condemned postmortem if there are visible lesions or tumors present on organs and carcasses. Of the more than 163 million cattle arriving at USDA-inspected slaughter facilities for the years 2003 through 2007, a total of 769,339 (0.47%) were condemned (White and Moore, 2009). Cattle fed or finished in feedyards, typically for 120 d before slaughter on high concentrate diets containing corn and soy as major ingredients, made up the majority (82%) of the cattle at harvest but represented a minority (12%) of the cattle condemned. Condemnation rates for non-fed cattle, particularly cows, were higher than for fed cattle, but the rate in 2007 (2.49%), the last year for which data are available, was similar to that reported in cattle in 1994 (2.6%; Boleman et al., 1998), before the introduction of GE crops.

The broiler data are particularly important due to the large number of animals involved (approximately 9 billion broilers are processed annually in the United States) and the fact that there are several variables that are indicative of health (Fig. 2). The rate of broiler carcass condemnation decreased significantly over time and was at its lowest in 2011. Moreover, mortality was essentially unchanged throughout the years presented and was also at its lowest in 2011. Although broilers are exposed to large amounts of corn and soybean meal during their 42- to 49-d lifespan, they increase their body size 60-fold during this period, making them very sensitive to

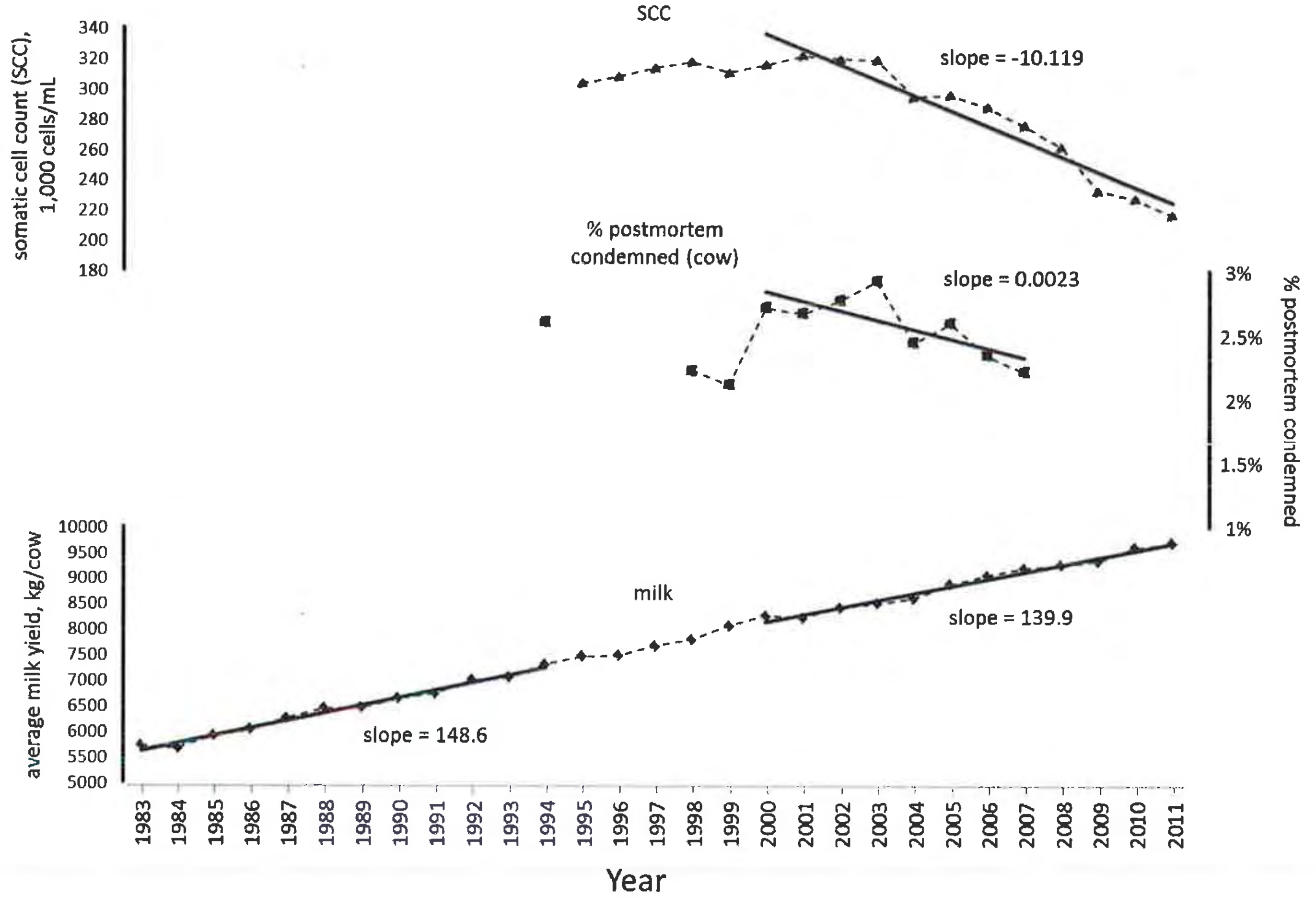

Figure 1. Milk production, percent postmortem condemned, and somatic cell counts for the United States before and after the introduction of genetically engineered crops in 1996. Sources: USDA National Agricultural Statistics Service, 2013; USDA Food Safety and Inspection Service, 2003; White and Moore, 2009; Boleman et al. (1998). Slope does not differ significantly between time periods 1983 through 1994 and 2000 through 2011.

dietary perturbations (European Food Safety Authority, 2008; International Life Sciences Institute, 2003). The conversion of feed to gain continuously decreased from 5 in 1985 to 3.8 in 2011, attributable most likely to improved genetics (Havenstein et al., 2003) and management, but this ratio is something that would be expected to worsen (i.e., increase) if the health of these animals was deteriorating following exposure to GE feed. An estimated 24 consecutive generations of broilers would have been consuming GE feed during the time period 2000 to 2011.

These field data sets representing billions of observations did not reveal unfavorable or unexpected trends in livestock health and productivity. The available health indicators from U.S. livestock suggest that these rates actually improved over time despite widespread adoption of GE crops in U.S. agriculture and increasing levels of GE content in livestock diets. There was no indication of worsening animal health after the introduction of GE feed, and productivity improvements continued in the same direction and at similar rates as those that were observed before the introduction of GE crop varieties in 1996.

A small number of experimental animal feeding studies have generated highly controversial results suggesting deleterious health effects of GE feed. Some of these reports were published and then retracted (Séralini et al., 2012), although recently and controversially republished without further peer review (Séralini et al., 2014), and others were never subjected to peer review (Ermakova, 2005; Velmirov et al., 2008). Adverse effects, including high rates of tumorogenesis, sterility, premature mortality, and histopathological abnormalities have been reported. These studies have been criticized for nonadherence to Organisation for Economic Co-operation and Development (Paris, France) consensus documents and standard protocols. Methodological flaws variously include the use of control feed that was not derived from near-isogenic lines, insufficient animal numbers to enable appropriate statistical power, lack of dose response or insufficient or no information on natural variations in test parameters, overinterpretation of differences that lie within the normal range of variation (i.e., the biological significance of differences is more important than their mere presence), and poor toxicological and/or statistical

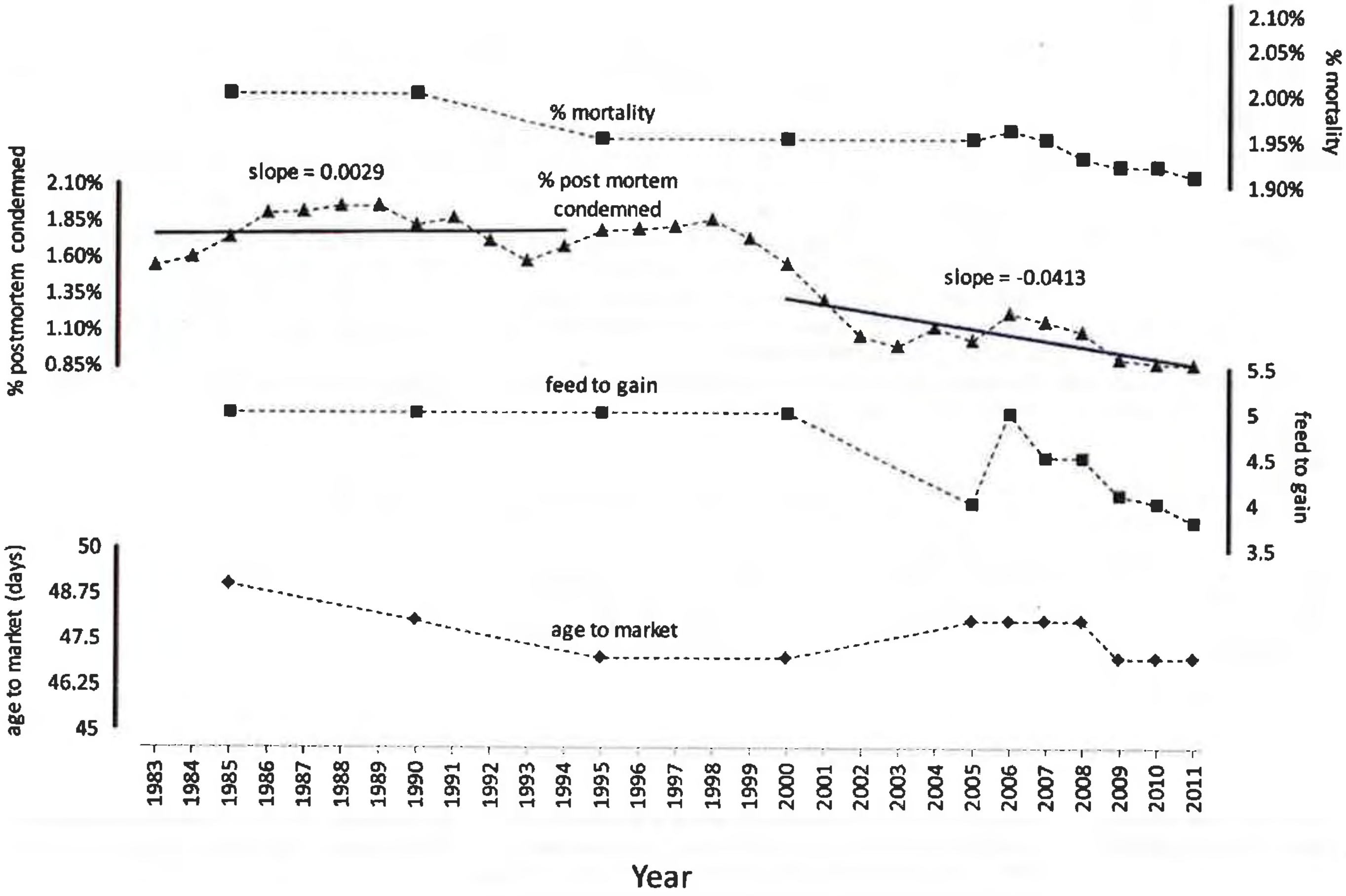

Figure 2. United States broiler statistics before and after the introduction of genetically engineered crops in 1996. Sources: USDA National Agricultural Statistics Service, 2013; National Chicken Council, 2011. Slope differs between time periods 1983 through 1994 and 2000 through 2011 (*$P < 0.05$).

interpretation of the data (Bartholomaeus et al., 2013; European Food Safety Authority, 2012; Marshall, 2007; Schorsch, 2013; The Australian and New Zealand Food Standards Agency, 2013, 2012). A particularly succinct summary of the methodological design flaws is presented in Table 5 (Bartholomaeus et al., 2013).

Despite a wealth of studies and literature to the contrary, these isolated and poorly designed studies have resulted in the promulgation of new regulations, including a mandatory 90-d rodent subchronic toxicity feeding study for all new GE approvals in the EU (Kuiper et al., 2013), and have generated a great deal of media attention (Arjó et al., 2013). They are also contrary to the field experience as documented by the health and production data collected on the billions of commercial food-producing animals that have primarily been consuming GE feed for over a decade. The media attention devoted to these sensational studies is exacerbating the continued controversy associated with the safety of GE food and feed and is bolstering arguments calling for the mandatory labeling of milk, meat, and eggs from GE-fed animals.

Summary of Data on Recombinant DNA/protein in Milk, Meat, and Eggs from Animals Fed Genetically Engineered Feed

Studies have concluded that animals do not digest transgenic and native plant DNA differently and that rDNA from GE crops has not been detected in animal products (Einspanier, 2013). Fragments of highly abundant plant DNA (e.g., chloroplast genomes) have been found in the digestive tracts and tissues of some species (Einspanier et al., 2001); however, neither recombinant DNA nor protein has ever been found in milk, meat, or eggs from animals that have eaten GE feed with the exception of a single study that reported the presence of fragments of transgenic DNA in both "organic" and "conventional" milk in Italy (Agodi et al., 2006). The organic milk was derived from animals not fed GE crops, so the authors postulated that the rDNA was due to feed and fecal contamination during milking of cows offered GE diets. This result has not been repeated despite recent studies using more sophisticated techniques that have looked for the presence of transgenic material in animal products (Buzoianu et al., 2012b; Deb et al., 2013; Guertler et al., 2010; Tufarelli and Laudadio, 2013). It is important to note that animals and humans regularly ingest DNA and

Table 5. Examples of limitations in experimental design, analyses, and interpretation in some whole food toxicity studies with genetically engineered (GE) crops (Bartholomaeus et al., 2013). Table reproduced with permission

Best practices	Deficiencies observed	References
Experimental design		
Identity of test and control substances	The identity of the GE test substance was not confirmed through an appropriate analytical method. Confirmation of correct control and test crop presence in diet was not conducted.	Brake and Evenson (2004), Ermakova (2005), Ewen and Pusztai (1999), Kilic and Akay (2008), and Malatesta et al. (2002a,b, 2003, 2005, 2008)
Use of appropriate control crops	The control crop was not of similar genetic background to the GE test crop. In some studies the control was simply identified as a "wild" variety.	Ermakova (2005), Ewen and Pusztai (1999), Malatesta et al. (2002a,b, 2003, 2005, 2008), and Rhee et al. (2005)
	The test and control substances were not produced under similar environmental conditions and/or no information was provided on the production of test and control substances.	Ermakova (2005), Ewen and Pusztai (1999), and Malatesta et al. (2002a,b, 2003, 2005, 2008)
Acceptable levels of contaminants (e.g., pesticides, mycotoxins, other microbial toxins) in control and test crops	Study results were not interpreted in light of differences in antinutrient or mycotoxin levels in test and control diets.	Carman et al. (2013) and Velmirov et al. (2008)
Nutritionally balanced diet formulations for control and test diets	Compositional analyses were not performed on the test and control substances to confirm that test and control diets had similar nutrient content and were nutritionally balanced.	Ewen and Pusztai (1999)
Description of study design, methods, and other details sufficient to facilitate comprehension and interpretation	Inadequate information was provided on the source of animals used, age, sex, animal husbandry practices followed, collection, and evaluation of biological samples to confirm that the procedures followed met accepted practices.	Ermakova (2005), Ewen and Pusztai (1999), and Séralini et al. (2012, 2014)
Statistical analyses and study interpretation		
Use of appropriate statistical methods for the design of the study	Statistical methods were sometimes not provided in sufficient detail to confirm if they were conducted appropriately for the data that were collected; statistical methods were documented but were not appropriate. Estimates of statistical power were based on inappropriate analyses and magnitudes of differences.	de Vendomois et al. (2009), Ewen and Pusztai (1999), Malatesta et al. (2003, 2005), and Séralini et al. (2007, 2012, 2014)
Appropriate interpretation of statistical analyses	Statistical differences were not considered in the context of the normal range for the test species, including data from historical and/or concurrent reference controls; the toxicological relevance of the difference was not considered (i.e., the reported finding is not known to be associated with adverse changes). Observed differences were not evaluated in the context of the entire data collected to determine if changes in a given parameter could be correlated with changes in related parameters.	Carman et al. (2013), de Vendomois et al. (2009), Ewen and Pusztai (1999), Kilic and Akay (2008), Malatesta et al. (2002a,b, 2003, 2005), and Séralini et al. (2007, 2012, 2014)
Adequate numbers of animals or test samples collected to be able to make meaningful comparisons between test and control groups	Too few animals/group were used to make meaningful comparisons; tissue sampling did not follow acceptable guidelines and was too limited to provide an accurate assessment of what was occurring in the organ being examined.	Ermakova (2005), Malatesta et al. (2002a,b, 2003, 2008), and Séralini et al. (2012, 2014)
Study publication and availability		
Publication of studies in peer-reviewed journals	Circumvention of the peer-review process removes a level of review that may contribute to ensuring that WF studies are appropriately designed and interpreted.	Ermakova (2005) and Velmirov et al. (2008)

RNA as part of traditional diets without consequence. The DNA from GE crops is chemically equivalent to DNA from other sources and both are thoroughly broken down in the gastrointestinal tract during digestion (Beever and Kemp, 2000; Jonas et al., 2001; CAST, 2006).

Intact recombinant proteins have never been detected in tissues or products of animals fed GE crops (Alexander et al., 2007). This is particularly important when considering the prospect of labeling secondary products such as milk, meat, and eggs. In some countries, mandatory food labeling regulations target the presence of GE components in the finished product (e.g., Australia, New Zealand, and Japan), whereas in other countries, regulations target foods that use GE technology as a part of the production process (e.g., the EU, Brazil, and China). It should be noted, however, that only Brazil currently requires mandatory labeling of products from animals that consume GE feed. Technically, the Brazilian law requires the label to state "(name of animal) fed with rations containing a transgenic ingredient" or "(name of ingredient) produced from an animal fed with a ration containing a transgenic ingredient.", but has yet to fully implement these laws. Given that there are no detectable and reliably quantifiable traces of GE materials in milk, meat, and eggs, any proposed labeling of animal products derived from GE-fed livestock would have to be based on documenting the absence of GE crops in the production chain, thereby necessitating the need for identity preservation and segregation requirements for producers and importers (Bertheau et al., 2009). This difference is important for verification: a product-based system can be enforced with testing equipment to analyze for the presence of GE materials and can filter a cheater, whereas a tracking system segregating indistinguishable products cannot guarantee the absence of products from animals that might have eaten GE feed (Gruère and Rao, 2007).

In 2012 the USDA's FSIS approved a voluntary process-based label for meat and liquid egg products that allows companies to label that they meet the Non-GMO Project's standard (<0.9% tolerance for GE presence) for the avoidance of GE feed in the diet of the animal producing the product. The FSIS allows companies to demonstrate on their labels that they meet a third-party certifying organization's standards, provided that the claims are truthful, accurate, and not misleading. A similar approach of certifying the absence of prohibited methods in the production chain, rather than testing for some quantifiable attribute in the end product, is used for other voluntary process-based labels such as certified organic and the USDA's Agricultural Marketing Service (**AMS**) Process Verified Never Ever 3 (**NE3**) Program which requires that animals are never treated with antibiotics or growth promotants or fed animal byproducts. Again, because the products raised using these methods are indistinguishable from conventional animal products, the USDA Process Verified Program ensures that the NE3 requirements are supported by a documented quality management system.

2013 Data on Global Production and Trade in Genetically Engineered Feedstuffs and Sources of Non-Genetically Engineered Feedstuffs

Global grain production is currently 2.5 billion t, of which approximately 12% (300 million t) is traded. Soy and corn make up two-thirds of global grain trade and these are the main players in commercial animal feed. Figure 3 illustrates the major global producers of these 2 crops and the proportion of global production that is from GE crop varieties. It is estimated that approximately 85% of soybean and 57% of corn grain production (USDA Foreign Agricultural Service, 2014b) are used in global livestock diets annually. The demand for livestock products has been increasing in response to population growth and income, particularly in developing countries. In Asia alone, consumption of meat and dairy products has been increasing annually by approximately 3 and 5%, respectively (Food and Agriculture Organization of the United Nations, 2012). Increase in demand for animal products, especially meat, will drive demand for grain and protein feeds (USDA Economic Research Service, 2008). The Food and Agriculture Organization of the United Nations (Rome, Italy) predicts that by 2050 global grain trade will double to 600 million t (Bruinsma 2009).

Of the protein sources available, soybean meal has one of the best essential AA profiles for meeting the essential AA needs of livestock and poultry. It is a good source of both lysine and methionine, which are the first limiting AA for swine and poultry, respectively. It is estimated that 79% (85 million ha) of global soybean hectarage is planted to GE varieties (Fig. 3). In 2013, 36.5% of global soybean production (97.2 million t) was exported and 97% came from 3 countries that grow GE soybeans—the United States, Brazil, and Argentina (Fig. 4).

Soybean meal is also an important component of animal feed globally (Fig. 5). In the 2011 to 2012 marketing year, domestic animal agriculture used 27.6 million t of U.S. soybean meal. Poultry continue to be the single largest domestic user of soybean meal, consuming about half of all meal, followed by swine. Soybean meal is a very important protein source for animal feeds in the EU, supplying 46% of the lysine supply overall. The EU imports 65% of its protein-rich feedstuffs, for which there are no alternative sources grown in the EU (Popp et al., 2013), and is the largest importer of soybean meal and the second largest importer of soybeans after China (Fig. 4 and 5). About 70% of soybean meal consumed in the EU is imported and 80% of this meal is produced from GE soybeans.

Corn is an important subsistence crop in many parts of the world and hence the majority of production is consumed within the country of production. Although only 32% (57 million ha) of global corn hectarage is planted with GE varieties (Fig. 3), 71% of global trade came from those countries that grow GE corn varieties (Fig. 6). Approximately 11.6% (100 million t) of global corn production was internationally traded in 2013. Three of the top 5 corn exporting countries—the United States, Brazil, and Argentina—currently grow GE corn. The remaining 2 countries—Ukraine and India—do not have officially registered and approved GE corn varieties.

Of the top 5 corn importing countries—Japan, Mexico, the EU, South Korea, and Egypt—only 5 countries within the EU (Spain, Portugal, Romania, Czechoslovakia, and Slovakia) grew a small amount (148,013 ha) of Bt-MON810 corn (USDA Foreign Agricultural Service, 2014a). Corn is the second largest category of GE products imported into the EU after soy. Unlike soybean, EU corn production is sufficient to meet most of its own corn consumption, with imports accounting for only 10% of total supply. Annual EU imports of corn products include US$1.8 billion of corn, $151 million of corn seed for planting, and $87 million of dried distillers grains (USDA Foreign Agricultural Service, 2013a).

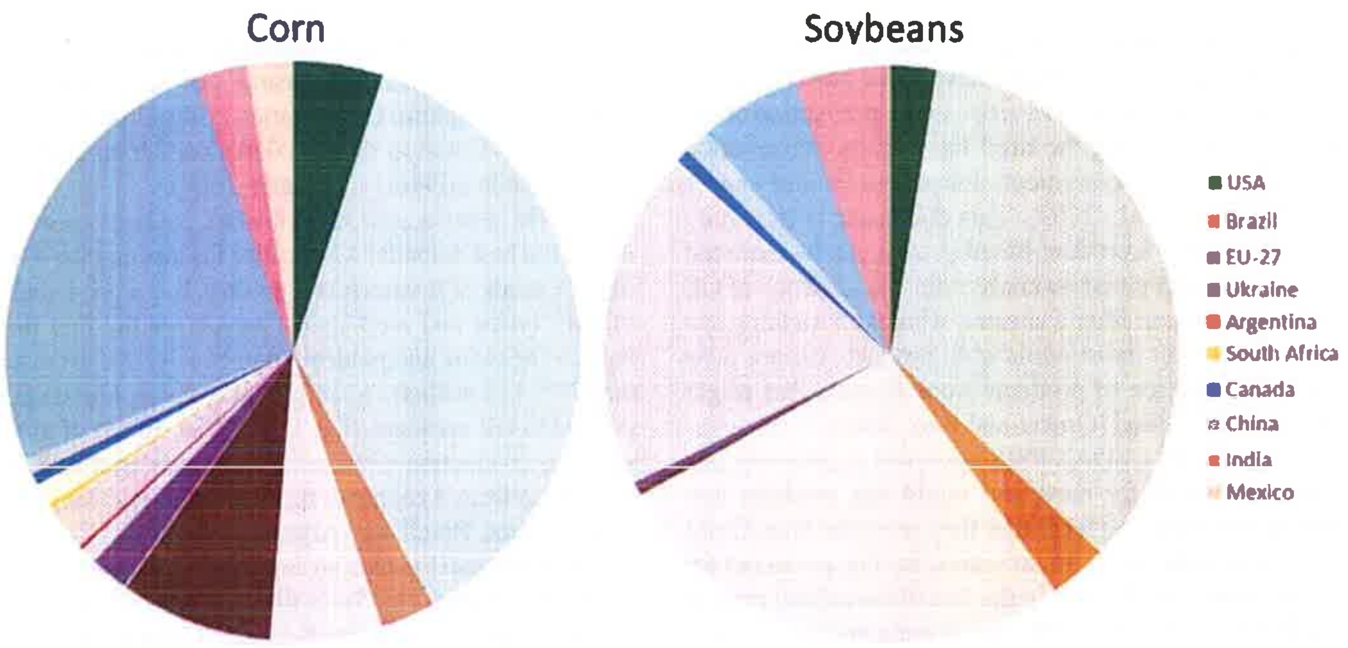

Figure 3. Genetically engineered (GE) and conventional corn and soy produced (million t) by selected countries 2012. Pattern represents production from GE varieties and solid slices represent conventional varieties. Sources: United States Department of Agriculture Foreign Agricultural Service; individual country Global Agricultural Information Network reports 2013; Food and Agriculture Organization of the United Nations (FAOSTAT). EU-27 = the 27 member states of the European Union (EU); production and trade database searches (faostat3.org/faostat-gateway/go/to/download/Q/*/E).

Prevalence of Markets Sourcing Non-Genetically Engineered Feed Globally for Livestock Populations as Compared to Conventional

World markets for grains can be separated into 4 segments: the conventional market (non-GE grain that is not certified as such), the mixed market (GE and conventional undifferentiated), the identity-preserved (certified non-GE) market, and the organic market. It is difficult to determine exact size estimates for these different markets, although it can be stated that the conventional and mixed markets are much larger than the remaining 2.

Of the top 5 soybean meal exporting countries in 2013—Argentina, Brazil, the United States, India, and Paraguay—only India does not allow the cultivation of GE soybeans. Of the top 5 soybean meal importing countries in 2013—the EU, Indonesia, Thailand, Vietnam,

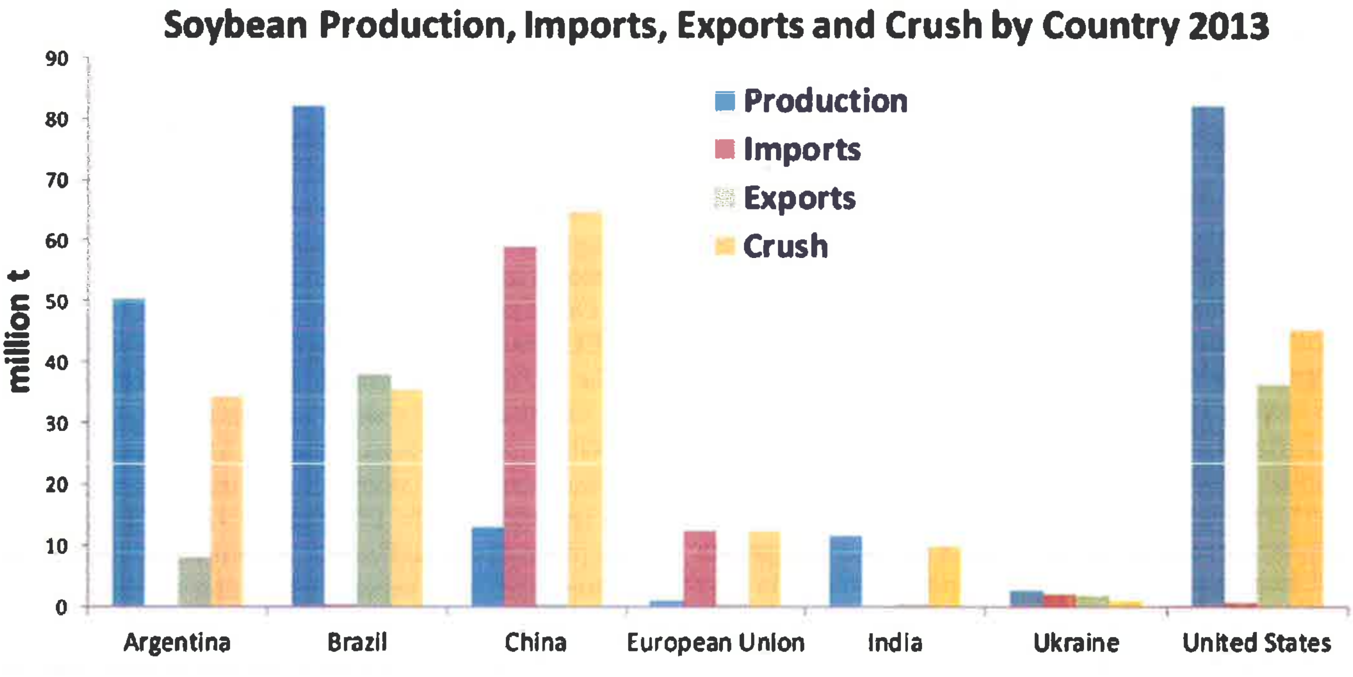

Figure 4. Soybean production, imports, exports, and crush (million t) by major import and export countries, 2013. Source: United States Department of Agriculture Foreign Agricultural Service; Production and trade database searches (http://faostat3.fao.org/faostat-gateway/go/to/download/G1/*/E).

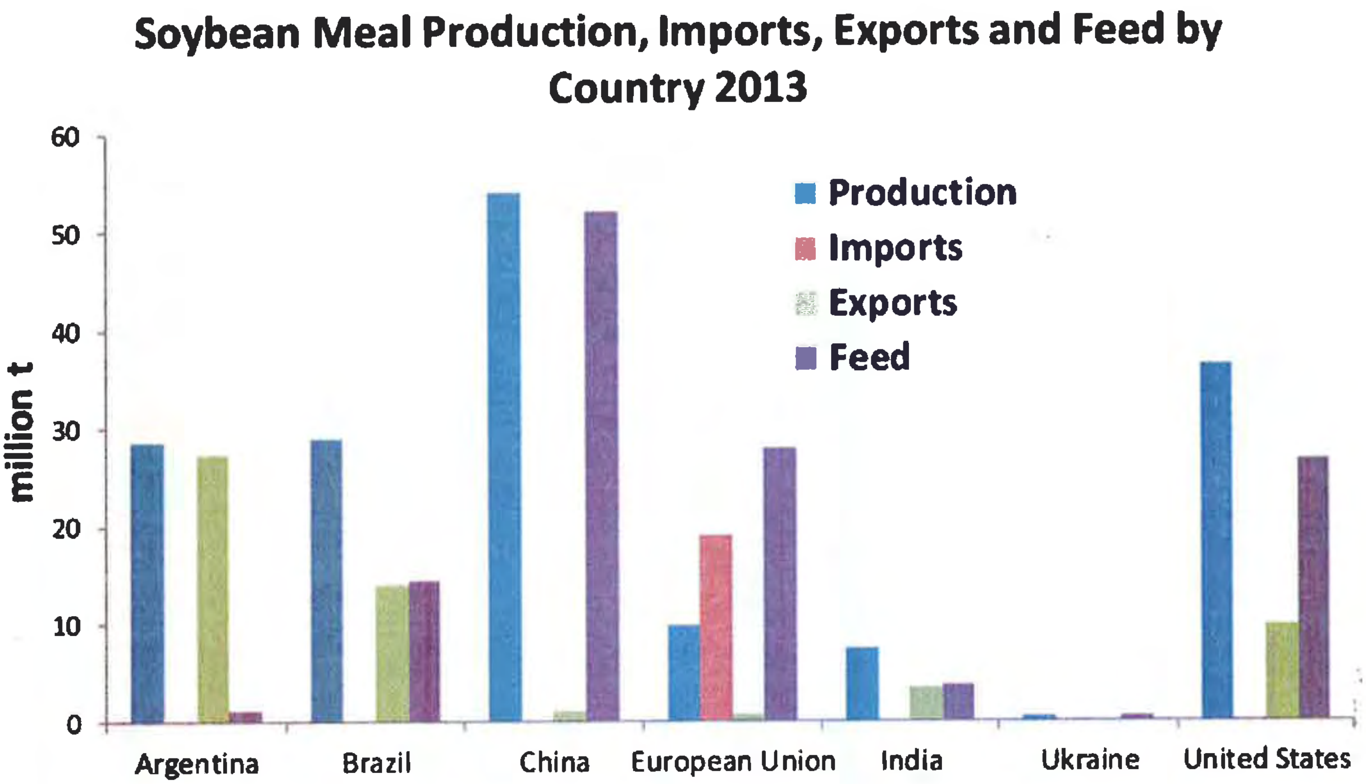

Figure 5. Soybean meal production, imports, exports, and feed (million t) by major import and export countries, 2013. Source: United States Department of Agriculture Foreign Agricultural Service; production and trade database searches (http://faostat3.fao.org/faostat-gateway/go/to/download/G1/*/E).

and Iran—none grow GE soybeans (USDA Foreign Agricultural Service, 2014a). It is estimated that between 4.0 and 4.5% of global trade in soybeans is required to be identity-preserved certified non-GE, and if it is assumed that this volume of traded soybeans is segregated from supplies that may contain GE soybeans, then the GE share of global trade is in the range of 93 to 96% (Table 6). A similar pattern occurs in soybean meal, where 88% of globally traded meal likely contains GE material (Table 7).

The estimated size of the export market requiring certified non-GE corn is 7.3 million t or 7% (Table 6). This excludes countries with markets for certified non-GE corn for which all requirements are satisfied by domestic production (e.g., corn in the EU). Farm animal feed in the 27 member states of the European Union (EU-27) is composed of 50% roughages and 10% grains produced on farm, 10% purchased feed materials, and 30% industrial compound feed. It has been estimated that in the EU, less than 15% of the animal feed market is identity-preserved certified non-GE, although there are great variations between countries. The main driver for non-GE feed is the poultry sector (17%) followed by the cattle (9%) and pig sectors (2%; European Feed Manufacturers' Federation, 2013).

The United States used to be a major supplier of corn to the EU in the 1990s but GE corn plantings in the United States caused a drastic decline in corn exports to the EU because of trade disruptions due to asynchronous approvals (i.e., cultivation approvals of specific GE varieties in the United States occurring before food and feed import approvals in the EU). The result is that the United States is no longer a major supplier of corn to the EU. Similarly, in 2007 there was a problem with asynchronous approval of a GE corn variety approved for cultivation in Argentina but unapproved for food and feed use in the EU. This concentrated demand on corn grown in Brazil, which increased prices an estimated €50/million t for compound feed producers in the EU (Popp et al., 2013).

China, which imported an estimated 5 million t of corn in 2013, making it the sixth largest corn importer, began rejecting shipments of U.S. corn in November 2013 after tests found a GE variety of corn that had been approved for cultivation in the United States, Argentina, and Brazil since 2011 but was not approved for food and feed import into China, despite a 2010 regulatory submission requesting such approval. China has a zero-tolerance policy for unapproved events. Since these trade disruptions began, a total of 3.3 million t of U.S. corn have been subject to rejection and diverted shipments (1.4 million t) or canceled or deferred sales. It has been estimated that up to $2.9 billion in economic losses were sustained by the U.S. corn, distillers' grains, and soy sectors in the aftermath of the zero-tolerance enforcement policy on U.S. export shipments to China (National Grain and Feed Association, 2014).

Interestingly, Ukraine signed a 3-yr agreement with China in 2013 for the delivery of 4 to 5 million t of corn

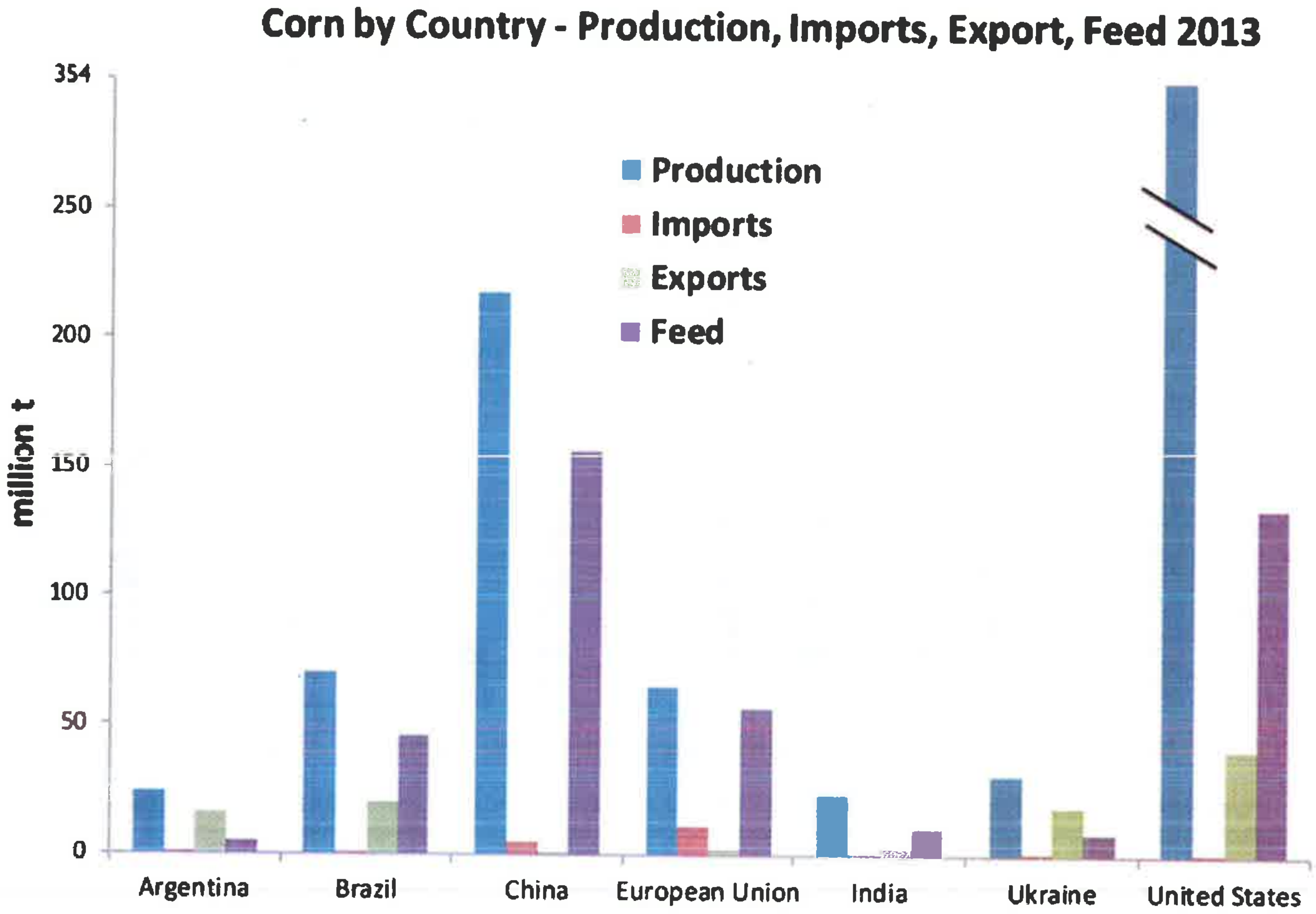

Figure 6. Corn production, imports, exports, and feed (production and trade database searches (http://faostat3.fao.org/faostat-gateway/go/to/download/G1/*/E)) by major import and export countries, 2013. Source: United States Department of Agriculture Foreign Agricultural Service; production and trade database searches(http://faostat3.fao.org/faostat-gateway/go/to/download/G1/*/E).

per year. Ukraine does not export or import GE products as none are officially registered and approved for commercial use or sale in the country. However, private sources estimate approximately 60% of the Ukraine soybean crop and 30% of the corn crop consist of GE varieties (USDA Foreign Agricultural Service, 2013b). China only accepts GE-positive cargo if the shipment is marked accordingly and contains only those GE events that are approved for import in China as well as cultivation in the country of origin. Given asynchronous regulatory approvals and the realities of agricultural production systems where harvesting machinery and storage facilities are shared among different production systems, trade disruption appears almost unavoidable if importing countries enforce a "zero-tolerance" policy for unapproved events that have been approved for cultivation in exporting countries.

Reliance on imported animal feed is becoming increasingly complicated for countries that wish to source non-GE products due to the significant GE adoption rate worldwide. In 2013, 4 major United Kingdom food supermarket groups—Tesco, Cooperative, Marks and Spencer, and Sainsbury's—ceased requiring that poultry and egg suppliers use only non-GE feed (Popp et al., 2013). Likewise, in 2014, the German poultry industry, which feeds 0.8 million t of soybean meal annually, abandoned its commitment to use only non-GE soybeans in poultry feed (USDA Foreign Agricultural Service, 2014c). This was largely due to the fact that Brazil is growing more GE soybeans and therefore has less identity-preserved certified non-GE soybeans available for export. As the global production of GE feed crops continues to rise, the EU's stringent GE tolerance levels (0.9% GE material limit plus 0.05% measuring uncertainty tolerance) and zero tolerance for unapproved events are complicating the maintenance of non-GE supply chains (Popp et al., 2013).

Current U.S. Options for Products from Non-Genetically Engineered Fed Livestock

Consumers wishing to purchase products from animals fed non-GE diets in the United States currently have that choice available through certified NOP products, the FSIS-approved Non-GMO Project verified label claim for meat and liquid eggs, and other non-genetically modified organism certification programs. Additionally, some private retailers are pursuing voluntary labeling.

Table 6. Share of global crop trade accounted for by genetically engineered (GE) crop production 2012/2013 (million t; Brookes and Barfoot, 2014c). Table reproduced with permission

Variable	Soybeans	Corn	Cotton	Canola
Global production	266	862.9	26.8	62.6
Global trade (exports)	97.2	100.1	10.0	12.0
Share of global trade from GE producers	94.6 (97.3%)	71.3 (71.2%)	6.9 (69%)	10.2 (85%)
Estimated size of market requiring identity-preserved (certified non-GE) market (in countries that have import requirements)[1]	4.0–4.5	7.3	Negligible	0.1
Estimated share of global trade that may contain GE (i.e., not required to be segregated)	90.1–93.2	64–92.8	6.9	10.1
Percentage of global trade that may be GE	92.75–95.9%	64–92.7%	69%	84.2–85%

[1] Estimated size of market requiring certified conventional in countries with import requirements excludes countries with markets for certified conventional for which all requirements are satisfied by domestic production (e.g., corn in the European Union [EU]). Estimated size of certified conventional market for soybeans (based primarily on demand for derivatives used mostly in the food industry): main markets: EU, 2.5 to 3.0 million t bean equivalents, and Japan and South Korea, 1 million t.

For example, in March 2013, the retail chain Whole Foods Market set a deadline that by 2018, animal products sold in its U.S. and Canadian stores must be labeled to indicate whether or not they came from animals that had consumed GE feed (Whole Foods Market, 2013). These voluntary process-based labels, in effect, verify that GE crops were not used in the production process, rather than testing for the presence of GE content in the animal products themselves as such products contain no detectable and quantifiable traces of GE materials.

Given the high rates of GE adoption in major feed crops, U.S. producers wishing to purchase non-GE feed for their livestock likely contract with growers or source identity-preserved (certified non-GE) or organic feed. In 2011, the United States had 1.26 million ha of certified organic cropland and 0.93 million ha of certified organic pasture and range (USDA National Agricultural Statistics Service, 2012). This translates into roughly 0.8 and 0.5% of total U.S. cropland and pasture/rangeland, respectively (Fig. 7). The availability and cost of certified organic feeds is a major challenge for U.S. organic livestock producers. The costs of certified organic feedstuffs are 2 to 3 times greater than non-organically-grown feeds (Hafla et al., 2013).

United States feed grain distributors and soy product manufacturers report sourcing organic soybeans from other countries. Organic farmers and handlers anywhere in the world are permitted to export organic products to the United States if they meet NOP standards and are certified by a USDA-accredited organic certification body. In 2007, USDA-accredited groups certified 27,000 producers and handlers worldwide to the U.S. organic standard, with approximately 16,000 in the United States and 11,000 in over 100 foreign countries (Grow and Greene, 2009). In 2007, approximately half of the accredited foreign organic farmers and handlers certified to NOP standards were in Canada, Italy, Turkey, China, and Mexico. Organic farming is often labor intensive, and developing countries with lower farm labor costs may have a competitive advantage in the production of some organic products.

In 2009, Canada was the main market for U.S. organic exports, while countries in Latin America, including Mexico, Brazil, Argentina, and Uruguay, along with China and other countries in Asia are major sources of organic imports (Grow and Greene, 2009). The countries with the fastest growth in organic production are those that produce organic products for export including China, Bolivia, Chile, Uruguay, and Ukraine. The amount of organic farmland increased well over 1,000% in these countries between 2002 and 2006, while organic farmland in Europe and North America showed slower (27–80%) expansion rates (Grow and

Table 7. Share of global crop derivative (meal) trade accounted by genetically engineered (GE) product 2012/2013 (million t; Brookes and Barfoot, 2014c). Table reproduced with permission

Variable	Soymeal	Cottonseed meal	Canola/rape meal
Global production	179.3	20.5	34.9
Global trade (exports)	57.2	0.6	5.6
Share of global trade from GE producers	50.4 (88%)	0.29 (46%)	3.6 (64%)
Estimated size of market requiring identity-preserved (certified non-GE) market (in countries that have import requirements)[1]	2.1	Negligible	Negligible
Estimated share of global trade that may contain GE (i.e., not required to be segregated)	48.3	0.63	3.6
Percentage of global trade that may be GE	84.4%	45%	64%

[1] Estimated size of certified conventional market for soymeal: European Union, 2 million t, and Japan and South Korea, 0.1 million t (derived largely from certified conventional beans referred to in Table 6).

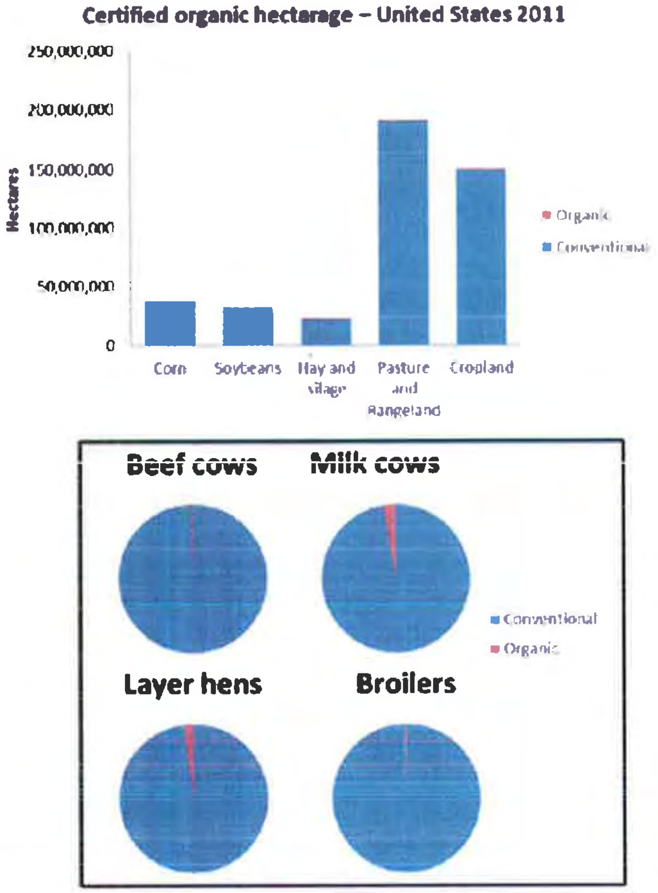

Figure 7. Certified National Organic Program hectarage and livestock numbers as a percentage of conventional U.S. numbers, 2011. Source: USDA National Agricultural Statistics Service, 2012. www.ers.usda.gov/datafiles/Organic_Produc tion/National_Tables_/CertifiedandtotalUSacreageselectedcropslivestock.xls. See online version for figure in color.

Greene, 2009). In 2013, the United States imported over $100 million of organic soybeans primarily from China and India (Fig. 8; Global Agricultural Trade System online [GATS] organic products www.fas.usda.gov/commodities/organic-products). The proportion of organic imports used for livestock feed versus human food purposes is unavailable as import product codes do not distinguish between these uses. Improved data collection is necessary to better describe international trade patterns in organic and identity-preserved (certified non-GE) feed.

Dairy

Organically raised livestock accounted for $1.31 billion in sales in 2011, the last year with a complete set of data on production and sales. Organic milk led livestock commodities, accounting for $765 million, or 58%, of organic animal product sales; however, less than 2% of U.S. dairy production is currently organic (Hafla et al., 2013). During 2011, approximately 254,700 dairy cows (2.78% of the total U.S. dairy herd; Table 2) on 1,848 dairy operations were certified organic. Production costs for organic dairies are greater than for conventional dairies due to the increased cost of organic feed and the increased use of labor and capital, which is not scale neutral as the total costs per unit of production drops sharply as herd size increases. Using pasture as a source of dairy forage is more common on organic dairies, which can help to reduce feed costs per cow but also contributes to lower production per cow. The U.S. organic dairy systems depend on the willingness of consumers to pay a premium (Hafla et al., 2013). The retail price for organic milk between 2004 and 2007 averaged 3 times the cost of conventional milk (USDA Economic Research Service, 2012b), and in 2013, organic milk made up 4.38% of total U.S. fluid milk market sales.

Beef

Natural, organic (grain-fed or otherwise), and grass/forage-fed (including cattle finished on grasses/forages to a specific quality standard) account for about 3% of the U.S. beef market (Mathews and Johnson, 2013). The term "natural" is not associated with an official production process standard so natural beef may come from animals that have consumed GE feed. Likewise, the USDA NE3 Process Verified Program does not mandate or specify the use of non-GE feed.

Beef from grass-fed ruminants can be labeled with a "grass (forage) fed" marketing claim through the AMS Process Verified Program if fed according to USDA standards. Under this verification standard, grass or forage must be the exclusive feed source throughout the lifetime of the ruminant animal except for milk consumed before weaning. The animal cannot be fed grain or any grain byproduct before marketing and must have continuous access to pasture during the growing season. However, silage is an accepted feed that can consist of relatively large portions of grain. For example, corn silage, which averages 10 to 20% grain and can consist of up to a third or more grain, blurs the distinction between grain fed and forage fed (Mathews and Johnson, 2013).

In a survey of certified organic beef producers in the United States, 83% reported that cattle were raised exclusively or predominantly on grass and hay until slaughter, while the remaining 17% reported using a grain finishing system (Hafla et al., 2013). Organic beef cattle may be finished in feedlots for no more than 120 d and must have access to pasture during this time. In 2011, 106,181 beef cows (0.34% of the total U.S. beef cows; Table 2) and 113,114 unclassified cows and young stock were raised in certified organic production systems. The price of natural/organic beef averaged

$12.08/kg in the first quarter of 2011, which represented a premium of $3.75/kg.

Poultry

The largest volume of organic meat sales is for poultry. In 2011, the number of certified organic broilers totaled more than 28 million (0.33% of the total U.S. broilers; Table 2), layer hens totaled more than 6.6 million (1.97% of the total U.S. layers), and turkeys totaled 504,000 (0.20% of the total U.S. turkeys). In 2011, sales of U.S. organic broilers and eggs totaled $115 million and $276 million, representing 0.5 and 3.7% of total sales, respectively. The retail price for organic poultry and eggs between 2004 and 2006 was approximately twice that of conventional products (USDA Economic Research Service, 2012a).

Currently, the size of the market for products derived from animals raised in production systems that use either identity-preserved certified non-GE or organic feed is less than 5% (Fig. 7). Voluntary labeling programs and market premiums exist for products derived from animals that have not consumed GE feed. Mandating the labeling of products derived from animals that have eaten GE-feed at the current time would result in labeling essentially all products derived from conventionally raised livestock (i.e., >95% of all animal products) in the United States.

If suppliers and marketers respond to mandatory labeling of products from animals fed GE feed by increasing the offering of products from animals fed non-GE feed, an increase in the non-GE feed supply would be required. This could come from non-GE feed sources (e.g., wheat and barley), from contracting with U.S. growers to plant non-GE crop varieties, or from imported feed sources. Reversion from GE to conventional crop varieties would require the adoption of altered agronomic practices to manage those crops and relinquishment of the documented environmental and economic benefits associated with the adoption of GE crops (Areal et al., 2013; Fernandez-Cornejo et al., 2014; Green, 2012; NRC, 2010). The prices received by U.S. non-GE corn and soybean producers in recent years have averaged 15% more than the prices received by conventional commodity producers (CAST, 2014), and globally traded non-GE soybean meal is roughly at a 13% premium to conventional soybean meal prices. Given the importance of feed costs in overall animal production costs, the cost of animal products from animals fed non-GE feed would be more expensive.

Impact of Genetically Engineered Feedstuffs on the Sustainability of Livestock Production

Feedstuffs are a major contributor to life cycle assessments in the production of meat, milk, and eggs on a national and global scale. By 2020, developing countries will consume 107 million t more meat and 177 million t more milk than the annual average of the years 1996 through 1998. The projected increase in livestock production will require annual feed consumption of cereals to rise by nearly 300 million t by 2020 (Delgado, 2003). Despite the fact that the first generation of GE crops with so-called "input" traits (those that potentially alter inputs needed in production) were not designed to increase crops yields per se, GE technology has added an estimated 122 and 230 million t to the global production of soybeans and corn, respectively, since the introduction of GE varieties in the mid 1990s (Brookes and Barfoot, 2014a).

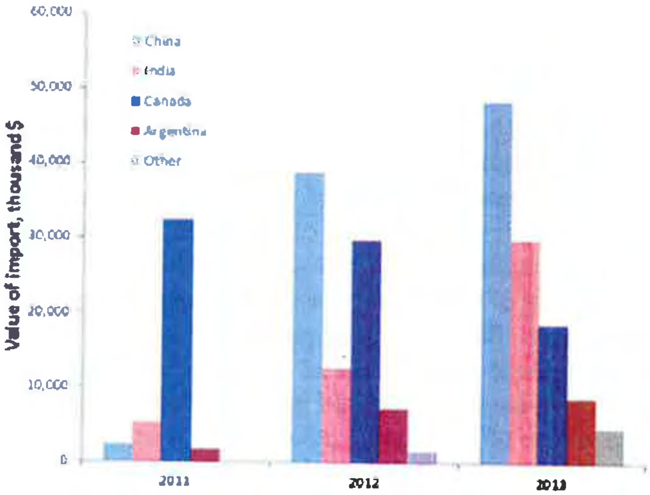

Figure 8. Value of certified National Organic Program soybeans imported into the United States, 2011 through 2013. Source: United States Department of Agriculture Foreign Agricultural Service (2014a). See online version for figure in color.

In 2013, approximately 175.2 million ha of GE crops were cultivated worldwide (James, 2013) by 18 million farmers. Over 90% (>16.5 million) were small-scale, resource-poor farmers in developing countries. This planting was greater than a 100-fold increase from the 1.7 million ha that were planted in 1996, making GE the fastest-adopted crop technology in recent history. India cultivated 11.0 million ha of Bt cotton with an adoption rate of 95%. In China, 7.5 million farmers cultivating an average of approximately 0.5 ha collectively grew 4.2 million ha of Bt cotton, an adoption rate of 90%. Farmers have planted these GE varieties to enable the adoption of improved agronomic practices (e.g., reduced insecticide applications) providing environmental, economic, and food security benefits in various countries (Ali and Abdulai, 2010; Burachik, 2010; Fernandez-Cornejo et al., 2014; Huang et al., 2010; Kathage and Qaim, 2012; Qaim and Kouser, 2013).

During the period 1996 through 2012, it has been estimated that the cumulative economic benefits from cost savings and added income derived from planting GE crops was $58.15 billion in developing countries and $58.45 billion in industrial countries (Brookes and

Barfoot, 2014a). The adoption of the technology also reduced pesticide spraying by 499 million kg (–8.7%), and has decreased the environmental impact of these crops by 18.1% (as measured by the indicator the Environmental Impact Quotient [a method that measures the environmental impact of pesticides]; Kovach et al., 1992) as a result of the use of less-toxic herbicides and reduced insecticide use (Brookes and Barfoot, 2014b). As a result of fuel savings associated with making fewer spray runs, the adoption of production systems with reduced tillage, and additional soil carbon sequestration, GE crops have also resulted in a significant reduction in the release of greenhouse gas emissions, which, in 2012 alone, was equivalent to removing 11.88 million cars from the roads (Brookes and Barfoot, 2014b).

Although some weed resistance has developed as a result of poor pest management practices and overreliance on a single herbicide (i.e., glyphosate), which may impact future benefits, the adoption of GE technology by the major livestock feed producing countries over the past 16 yr has had a positive sustainability outcome both in terms of increased global yield as a result of improved pest control and reduced overall environmental impacts per kilogram of animal feed produced.

The Future

There are numerous GE crops enhanced for animal nutrition in the research and development pipeline, with almost 100 events under research in many countries of the world (Tillie et al., 2013). This reflects both the importance of feed markets for GE crops and the potential nutritional improvements that can be brought to the quality of feedstuffs using this technology. There are 2 ways in which plant breeding might increase the efficiency of livestock production; the first is by raising the crop yield per hectare (e.g., improved drought tolerance or N use efficiency) and the second is by improving the rate of conversion of vegetable calories into animal calories (e.g., altered output traits or crop composition). Genetic engineering offers new possibilities for approaching both of these objectives, including improving the nutritional value of feed (e.g., AA content; Huang et al., 2006), lowering N and P pollution through altered crop composition (e.g., low phytate; Chen et al., 2008), and reducing manure excretion through a higher NE value (e.g., reduced lignin; Jung et al., 2012). Several of these crops are far advanced in the regulatory pipeline (Table 8; Tillie et al., 2013)

These so-called "second generation" crops modified for output traits will pose some regulatory and commercialization challenges. The first is that they will not, by definition, be substantially equivalent to isogenic non-GE varieties. Protocols have been developed to address the safety testing of these crops (International Life Sciences Institute, 2007). However, given the different regulatory approaches that are in place for crops that are compositionally equivalent, it is unclear how regulatory requirements may vary between countries in terms of the number and length of target animal feeding studies for these crops with altered output traits. Additionally, if the benefits derived from growing these crops accrue to the livestock producer or feeder and not directly to the farmer growing the crop, there will need to be some form of supply chain segregation in place to ensure a price premium is obtained for the value-added output trait.

An additional concern is the increasing problem of asynchronous regulatory approval, or regulatory asynchronicity. Currently, 33 countries have regulatory systems that handle approval for the cultivation or importation of new GE crops (International Service for the Acquisition of Agri-Biotech Applications, 2014). There are considerable discrepancies in the amount of time required to review and approve new GE crops in different countries. This leads to a situation where GE crops may be cultivated and marketed in some countries and remain unapproved in others. As discussed previously, this has resulted in trade disruptions, especially when countries use a "zero-tolerance" policy for unapproved events, meaning that even minute traces of unapproved GE crops are illegal and must be withdrawn from the market. Under a zero-tolerance policy, trade of relevant commodities between asynchronous countries will likely cease as importing and exporting firms will act to avoid the risk associated with a positive test (Kalaitzandonakes et al., 2014). Countries with zero-tolerance policies will be perceived as risky export markets, and importers will pay higher prices and insurance premiums to offset risks taken by the supplier.

Currently, the most accepted techniques for the detection of rDNA and protein products are PCR and ELISA, respectively. Various analytical methods have been developed and are routinely used for the monitoring of GE origin in raw materials and processed foods and have been reviewed elsewhere (Alexander et al., 2007; Marmiroli et al., 2008). Although efforts have been taken to harmonize analytical methodology for the detection of GE products at national, regional, and international levels, no international standards have yet been established (Holst-Jensen et al., 2006). Sampling, testing, and certification depend on statistical processes, however, and hence all are subject to some error, which increases at very low tolerances (Lamb and Booker, 2011).

Kalaitzandonakes et al. (2014) succinctly summarizes some emerging trends in terms of likely increased regulatory asynchronicity in the future. These include 1) the expanding pipeline of novel GE crop events, including second generation crops modified for output traits; 2) the expanding range of GE crop species being grown and

Table 8. Summary of genetically engineered crops modified for output traits in the latest stages of the pipeline. Modified from Tillie et al. (2013).

Crop	Identifier	Stage[1]	Commercial name	Trait	Developer[2]	Regulatory approval status					
						United States	Argentina	Brazil	China	European Union	Japan
Soybean	DP-305423-1	1	Treus-Plenish	High oleic acid	Pioneer	All uses – 2009	None	None	Food and feed – 2011 (expires 2014)	Food and feed application; additional data request – 2012	All uses – 2010
Safflower		1	Sonova 400	Omega-6	Arcadia BioSciences	Grown under permit; dietary supplement	None	None	None	None	None
Corn	BVLA430101	2		Phytase expression	CAAS/Originally in Agritech	None	None	None	None	None	Cultivation – 2009
Corn	REN-00038-3	2	Mavera	High lysine	Monsanto	All uses – 2006	None	None	None	Application withdrawn – 2009	All uses – 2007
Corn	REN-00038-3 × MON00810-6	2	Mavera YieldGard	High lysine + herbicide tolerance	Monsanto	All uses – 2006	None	None	None	Application withdrawn – 2009	All uses – 2007
Soybean	DP-305423-1 × MON04032-6	2		High oleic acid + herbicide tolerance	Pioneer	All uses – 2009	None	None	None	Food and feed application; additional data request – 2012	All uses – 2012
Soybean	MON-87705-6	2	Vistive Gold	High oleic acid	Monsanto	All uses – 2011	None	None	None	Imports and domestic use – 2012	Food and feed – 2013
Soybean[3]	DD-026005-3	2		High oleic acid	Pioneer	All uses – 1997	None	None	None	None	All uses – 2007
Alfalfa	MON-00179-5	3	None	Low lignin	Forage Genetics/ Monsanto	Food and feed – 2013	None	None	None	None	None
Rapeseed	MPS961-5	3	PhytaSeed	Phytase expression	BASF	Food and feed – 1999	None	None	None	None	None
Soybean	MON87769	3	None	Omega-3	Monsanto	All uses– 2011/2012	None	None	None	Food and feed application; additional data request – 2012	None

[1] Development stage: 1 = commercialized; 2 = commercial pipeline; 3 = regulatory pipeline.

[2] Pioneer, Johnston, IA; Arcadia Biosciences, Davis, CA; CAAS, Beijing, China; Monsanto, St. Louis, MO; Forage Genetics, Nampa, ID; BASF, Ludwigshafen, Germany.

[3] Events whose development is currently discontinued. The information regarding the regulatory status of the events reported in this table was updated in May 2014.

traded; 3) the expanding global hectarage of GE crops and the growing number of countries that raise them; and 4) the nascent and inexperienced regulatory expertise in many countries that will be called on to manage a large number of regulatory submissions for new GE crops in the future. Given the scope of trade of livestock feedstuffs and the increasing importance of GE crops in this supply, trade disruptions appear imminent, especially in countries that have slow approval processes for GE imports and yet are heavily dependent on commodity imports from exporting countries that are cultivating and developing a large number of GE crop varieties.

The emergence of precise gene-editing technologies (e.g., zinc finger nucleases [ZFN], meganucleases, transcription activator-like effector nucleases [TALEN], oligonucleotide-directed mutagenesis, and clustered regulatory interspaced short palindromic repeat [CRISPR]/ Cas-based RNA-guided DNA endonucleases) that enable targeted editing of specific nucleotides in the endogenous genome (Kim and Kim, 2014) will further complicate this situation. Gene editing could be considered a form of directed mutagenesis and it is unclear whether gene-editing technologies for crops and animals will be encompassed by the GE regulatory system. This is especially uncertain where gene editing results in the substitution of 1 naturally occurring allelic form of a gene for another of the same gene or induces a mutation in an existing gene through a single base pair change analogous to the spontaneous mutation process (Wells, 2013). Whether these types of modifications should be subject to regulation is a topic of discussion among the global regulatory community (Bruce et al., 2013; Hartung and Schiemann, 2014; Lusser and Davies, 2013). Given that the regulatory process takes years and costs millions of dollars (Prado et al., 2014), the governance of emerging gene-editing technologies will have a great influence on the future development of crops carrying these genetic modifications and will significantly impact the ability of the public sector and small companies to bring gene-edited products to market.

Of particular practical importance is that there will be no way to differentiate a gene-edited DNA alteration from a naturally occurring mutation and hence no way to trace and track "genetically modified" gene-edited crops or differentiate them from genetic modifications resulting from spontaneous mutations. Many of the existing PCR-based tests for GE crops are designed using primers that amplify unique DNA sequences that are common to a variety of transgenic crops (e.g., exogenous promoter sequence or gene coding sequence). As new GE crops with multiple novel regulatory and coding region sequences are developed, it will be increasingly difficult to use PCR-based assays to detect all possible events. Furthermore, PCR-based screening methodology may be unable to detect the genetic modifications that are under development through precise breeding techniques (Lusser et al., 2012). Likewise, some gene-editing techniques generate genetic changes that cannot be distinguished from conventionally bred crops or from crops produced by natural genetic variation or unregulated radiation mutagenesis (Broeders et al., 2012). Process-based regulatory frameworks that rely on PCR-based detection of specific transgenic constructs will be unable keep pace with technological developments when the products of these advanced breeding techniques are indistinguishable from those produced using conventional breeding techniques.

These developments may lead to a revaluation of the current rDNA process-based regulatory trigger for GE organisms to a more scientifically defensible product-based approach centered on the novelty and any unique risks associated with the phenotype of the product rather than the process used to accomplish the genetic modification (Bradford et al., 2005; McHughen, 2007). The need for international coordination and synchronization of regulatory frameworks for GE products is becoming increasingly urgent as both research and development of GE crops and animals are proceeding at an accelerated rate in an ever increasing number of countries in the world. In the absence of international harmonization, costly trade disruptions are likely to become increasingly widespread in the future to the detriment of global food security.

Conclusions

Commercial livestock populations are the largest consumers of GE crops, and globally, billions of animals have been eating GE feed for almost 2 decades. An extensive search of peer-reviewed literature and field observations of animals fed diets containing GE crop products have revealed no unexpected perturbations or disturbing trends in animal performance or health indicators. Likewise, it is not possible to distinguish any differences in the nutritional profile of animal products following consumption of GE feed. Animal agriculture is currently highly dependent on GE feed sources, and global trade of livestock feed is largely supplied by countries that have approved the cultivation of GE crops. Supplying non-GE-fed animal products is likely to become increasingly expensive given the expanding global planting of GE crops and the growing number of countries that raise them. The market for animals that have not consumed GE feed is currently a niche market in the United States, although such products are available to interested consumers via voluntary process-based marketing programs. The cost of these products is higher than conventionally produced products due to both the higher cost of non-GE feed and the costs associated with certifying the absence of GE crops in the production process and product segregation. There is currently a pipeline of so-called "second generation" GE crops with improved output traits for livestock production. Their approval will further complicate the sourcing of non-GE feedstuffs. Additionally, recent developments in techniques to induce precise genetic changes in targeted genes offer both tremendous opportunities and a challenge for global regulatory oversight. Given these developments, there is an urgent need for international harmonization of both regulatory frameworks for GE crops and governance of advanced breeding techniques to prevent widespread disruptions in international trade of livestock feedstuffs in the future.

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Weed control changes and genetically modified herbicide tolerant crops in the USA 1996–2012

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Abbreviations: EIQ, environmental impact quotient; GFK, GFK Crop and Animal Health Company; GM, genetically modified; HT, herbicide tolerant; Kg, kilogram; $ US United States dollar; USDA NASS, United States Department of Agriculture National Agricultural Statistics Service

Crops that have been genetically modified (GM) to be tolerant to herbicides have been widely grown in the USA since 1996. The rapid and widespread adoption of this technology reflects the important economic and environmental benefits that farmers have derived from its use (equal to $21.7 billion additional farm income and a 225 million kg reduction in herbicide active ingredient use 1996–2012). During this time, weed control practices in these crops relative to the 'conventional alternative' have evolved to reflect experience of using the technology, the challenges that have arisen and the increasing focus in recent years on developing sustainable production systems. This paper examines the evidence on the changing nature of herbicides used with these crops and in particular how farmers addressed the challenge of weed resistance. The evidence shows that use of the technology has resulted in a net reduction in both the amount of herbicide used and the associated environmental impact, as measured by the EIQ indicator when compared to what can reasonably be expected if the area planted to GM HT crops reverted to conventional production methods. It also facilitated many farmers being able to derive the economic and environmental benefits associated with switching from a plough-based to a no tillage or conservation tillage production system. In terms of herbicide use, the technology has also contributed to a change the profile of herbicides used. A broad range of, mostly selective herbicides has been replaced by one or 2 broad-spectrum herbicides (mostly glyphosate) used in conjunction with one or 2 other (complementary) herbicides. Since the mid-2000s, the average amount of herbicide applied and the associated environmental load, as measured by the EIQ indicator, have increased on both GM HT and conventional crops. A primary reason for these changes has been increasing incidence of weed species developing populations resistant to herbicides and increased awareness of the consequences of relying on a single or very limited number of herbicides for weed control. As a result, growers of GM HT crops have become much more proactive and diversified in their weed management programs in line with weed scientist recommendations and now include other herbicides (with different and complementary modes of action) in combination with glyphosate, even where instances of weed resistance to glyphosate have not been found. The willingness to proactively diversity weed management systems in the GM HT crops is also influenced by a desire to maintain effective weed control and hence continue to enjoy the benefits of no tillage and conservation tillage. Nevertheless, despite the increase in herbicide use in recent years, the use of GM HT technology continues to deliver significant economic and environmental gains to US farmers.

Decreased herbicide use, increase in no-till

Introduction

Crops that have been genetically modified (GM) to be tolerant to herbicides (mostly to the herbicide glyphosate but also including tolerance to glufosinate) have been widely grown globally and in the USA since 1996. GM herbicide tolerant (HT) soybeans were first grown commercially in 1996, followed by GM HT corn and cotton in 1997, canola in 1999 and sugar beet in 2007. Adoption of this technology has been rapid, and by 2013, the US planted area reached 62.1 million hectares (Brookes and Barfoot (2014a[1] and James (2013[2])).

In terms of the share of the 5 arable crops in which GM HT technology have been commercialised, GM HT traits accounted for 88% of the total US plantings to these 5 crops in 2013 (there

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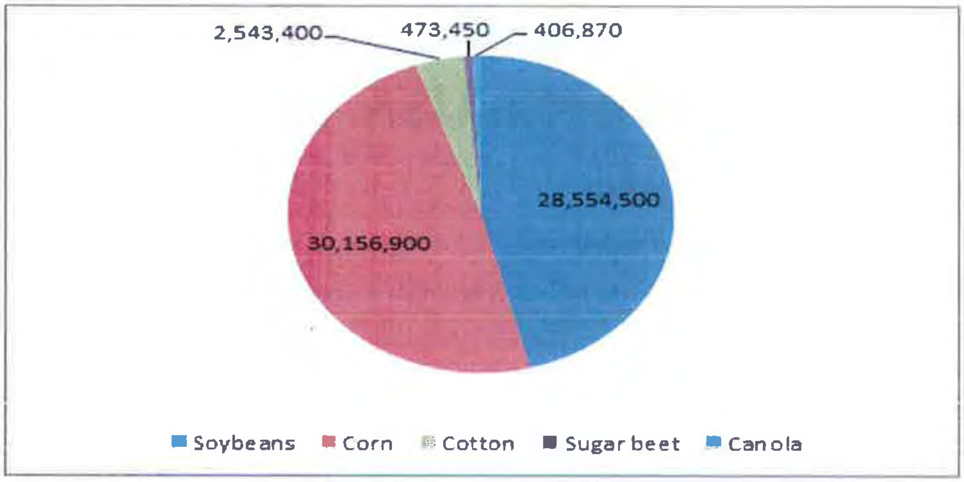

Figure 1. United States GM HT crop plantings 2013 by crop (hectares).Sources: derived from USDA, ISAAA, GfK Animal and Crop Health
Note: Base area of the 5 crops 62.1 million ha.

were also additional GM HT crop plantings of about 700,000 ha of alfalfa). In 2013, GM HT corn accounted for the largest share (49%), followed by soybeans (46%) and cotton (4%: Fig. 1).

In relation to the share of total US plantings to each of these crops, GM HT traits accounted for 90% of soybean plantings in 2013. For the other crops, the GM HT shares in 2013 were 85% for corn, 82% for cotton, 93% for canola and 98% for sugar beet.

The rate of adoption and use of GM HT technology in US agriculture since the mid-1990s has been rapid and widespread largely because of the benefits farmers have derived from its use. In the period 1996 to 2012, the total US farm income benefit from using the technology amounted to $21.7 billion. These gains mostly derived from reductions in the cost of production. In addition, the technology has delivered important environmental benefits through a reduction in the volume of herbicides used (225 million kg of active ingredient use 1996–2012: Brookes and Barfoot (2014b[3])), a change in the profile of herbicides used (to ones which are more environmentally benign than those replaced) and through the facilitation of changes from a conventional plough-based to a no tillage or conservation tillage production system for many farmers. This change in production system has made additional positive economic contributions to farmers (and the wider economy) and delivered important environmental benefits, notably reduced levels of greenhouse gas (GHG) emissions (from reduced tractor fuel use and additional soil carbon sequestration), reduced soil erosion and increased soil water conservation (Brookes and Barfoot (2014b[2]).

Against this background, this paper examines the nature of herbicide-based weed control practices (the main form of weed control) in these crops relative to the 'conventional alternative' since their adoption and how these practices have evolved to reflect experience of using the technology, the challenges that have arisen and the increasing focus in recent years on developing sustainable production systems. The introduction of GM HT crops occurred at a time when the emergence of weed species resistant to some widely used herbicides was already affecting and limiting farmers' choice of herbicides. In addition, the scope for farmers' using no tillage and conservation tillage practices consistently was constrained by difficulties in obtaining good weed control with the existing herbicides available. As farmers increasingly adopted GM HT technology they also had to address the number of weed species resistant to the herbicides that the crops were genetically modified to be tolerant to, learn how best to minimize this occurrence and develop a sustainable, longer term weed management systems applicable to all forms of arable crop production in the USA.

Methodology

Data availability and limitations

The analysis presented is based on an extensive examination of existing farm level herbicide usage data for both GM HT and conventional crops in the USA. Assessment of the impact of the technology on herbicide use requires comparisons of the weed control measures used on GM versus the 'conventional alternative' form of production. This presents a number of challenges relating to both availability of data and the representativeness of the available data.

Comparison data ideally derives from farm level surveys which collect usage data on the different forms of production. A search of the literature on herbicide use change with GM HT crops shows that while there are a number of studies exploring this issue, few provide data to the herbicide (active ingredient) level. Secondly, publicly available, national level herbicide usage survey data is incomplete, and of limited value. The United States Department of Agriculture's National Agriculture Statistical Service (USDA NASS) undertakes farm level surveys of herbicide use in field crops. However, while in the past these were conducted on an annual basis for the main field crops, for several years now, these surveys have only been conducted periodically. For example, herbicide use in soybeans was reported annually until 2006 and since then has only been surveyed in 2012; in corn, annual usage was recorded to 2003 and since then only 2005 and 2010 data have been collected. Similarly, recent herbicide usage data on the US cotton crop has only been collected in 2007 and 2010. In addition, the number of states from which data was collected varied from year to year for each crop and this lack of consistency results in an irregular data set and therefore limits the conclusions that can be drawn from the data. Furthermore, this USDA dataset is of limited value for assessing differences in herbicide usage on GM HT and conventional crops because the data is not disaggregated into use with these 2 different forms of production. The only comprehensive source of data on herbicide use to the active ingredient level, collected on an annual basis in the US, based on farm level survey data, is from the private market research company Gfk Animal and Crop Health. This publicly available on subscription data set, widely used by many in the agricultural inputs sector, has been a primary resource used for this paper, and much of the analysis presented draws from this resource.

Nevertheless, it is important to recognize that even this dataset has limitations. To estimate the changes in amount of herbicide used with GM HT crop technology, requires an assessment of what herbicides might reasonably be expected to be used in the absence of GM HT technology on the relevant crops (in other words, if the entire crops used conventional (non GMO) production methods). The Gfk data set provides usage rates for the area planted to conventional crops, however, as the GM HT area increased, the area remaining in conventional crops became a relatively small share of the total crop area. The conventional share (not using GM HT technology) of each crop is currently very small and has remained so for a number of years. For example, the share of the total planting area accounted for by conventional crops (non GM) has been below 50% of the total since 1999 in respect of soybeans, since 2001 for cotton and canola, since 2007 for corn and 2008 for sugar beet. The conventional cropping data set is therefore unrepresentative of the levels of herbicide use that might reasonably be expected across the whole crop in the absence of GM HT technology and hence utilizing this limited data is likely to produce biased results – in other words there is self-selection bias. There are several reasons for this:

- While the degree of weed problems vary by year, region and farm, some farmers who continue to farm conventionally may have relatively low levels of weed problems, and hence see little, if any, benefit from using the GM HT traits. Their herbicide usage is typically below the levels that would reasonably be expected on an average farm with 'average' weed problems;
- Some of the farms that continue to use conventional seed apply production methods (including organic) which feature limited (below average) use of herbicides, increased reliance on tillage practices and increased labor inputs to manage weeds. The usage patterns of this sub-set of growers will understate usage for the majority of farmers if they all returned to farming without the use of GM HT technology;
- Some of the farmers using GM HT technology have experienced improvements in weed control from using this technology relative to the conventional control methods previously used. If these farmers were to now revert to using conventional techniques, it is likely that most would wish to maintain the levels of weed control efficacy obtained with GM HT technology and therefore may use more herbicides than they did in the pre-GM HT crop days.

Overcoming data limitations: making representative comparisons

To address the problem of bias and poor representativeness of herbicide usage data for the conventional crop system if GM HT technology was not available, the herbicide usage data were adjusted based on input from weed scientists. Firstly, average recorded values for herbicide usage on conventional crops were used only for years when the conventional crop accounted for more than 50% of the total crop area. Secondly, in other years – when the conventional crop area fell below 50% of the total crop area (e.g., in the US from 1999 for soybeans, from 2001 for cotton and from 2007 for corn) – estimated values were used based on input from extension and industry advisors across the US of the likely usage if the whole US crop was no longer using crop biotechnology. Finally, the usage levels identified from this methodology were cross checked (and subject to adjustment) against historic average usage levels of key herbicide active ingredients from the Gfk dataset so as to minimize the scope for understating or overstating likely usage levels on the conventional alternative.

This methodology, used by others (e.g., Sankala and Blumenthal (2003[4])) has the advantage of providing representative comparisons of current weed control practices on both GM HT crops and the conventional alternatives. Importantly, it takes into account dynamic changes in weed management practices (e.g., adapting to no-till and conservation tillage practices, controlling resistant weed species and responding with more diversified, sustainable weed management practices) and technologies (e.g., new herbicides) rather than making comparisons solely on past practices.

Assessing the environmental impact of herbicide use

The most common way that environmental impact associated with herbicide use changes with GM HT crops has been presented in the literature has been in terms of the volume (quantity) of pesticide applied. However, while the amount of pesticide applied to a crop is one way of trying to measure the environmental impact of pesticide use, this is in fact not a good measure of that parameter because the toxicity and risk of each pesticide is not directly related to the amount (weight) applied. For example, the environmental impact of applying one kg of dioxin to a crop or land is far more toxic than applying 1 kg of salt. There exist alternative (and better) measures that have been used by a number of authors of peer reviewed papers to assess the environmental impact of pesticide use change with GM crops rather than simply looking at changes in the volume of active ingredient applied to crops. In particular, there are a number of peer reviewed papers that utilize the Environmental Impact Quotient (EIQ) developed at Cornell University by Kovach et al. (1992[5]) and updated annually. This effectively integrates the various environmental impacts of individual pesticides into a single 'field value per hectare'. The EIQ value is multiplied by the amount of pesticide active ingredient (ai) used per hectare to produce a field EIQ value. For example, the EIQ rating for glyphosate is 15.33. By using this rating multiplied by the amount of glyphosate used per hectare (e.g., a hypothetical example of 1.1 kg applied per ha), the field EIQ value for glyphosate would be equivalent to 16.86/ha. In relative terms, products with higher field EIQ/ha values represent a potential increase in environmental concern and may require more care in how they are used.

The use of environmental indicators is now increasingly being used by researchers to assess the impact of changes in pesticide usage and the EIQ indicator has been used by a number of researchers to examine the environmental impact of pesticide use changes with GM crops (e.g., Brimner et al. (2004[6]), Kleiter et al. (2005[7])). This analysis uses the EIQ indicator, a comparison of the field EIQ/ha for the conventional vs. GM HT crop production systems, which takes into account the total environmental impact or load of each system, derived from the respective field EIQ/ha values and the area planted to each type of production (GM versus conventional). The EIQ indicator provides an improved assessment of the impact of GM crops on the environment when compared to only examining changes in volume of active ingredient applied, because it draws on some of the key toxicity and environmental exposure data related to individual products, as applicable to impacts on farm workers, consumers and ecology.

In the present paper, the EIQ indicator is used in conjunction with examining changes in the volume of herbicide active ingredient applied. Readers should, however, note that the EIQ is an indicator only (largely one of toxicity) and does not take into account all environmental issues and impacts. It is therefore not a comprehensive indicator.

Weed Control Practice Evolution in the US since the Introduction of GM HT Technology

GM HT (to glyphosate) soybeans

In the early years of adoption of GM HT soybeans, the primary weed control practice used was an almost total dependence on glyphosate, typically a single or 2 in-crop treatments, often in conjunction with the adoption of reduced or no tillage production system. For example, in 1998, glyphosate accounted for over 80% of total herbicide active ingredient use on GM HT soybeans. This compared with conventional soybeans, where a broader range of selective herbicides, of which chlorimuron, imazamox, imazethopyr, pendamethalin and trifluralin were the most commonly used, were typically applied in several treatments. As a result, in the early years of adoption, the average amount of herbicide applied to the GM HT soybean crop tended to be higher than the amount typically applied to the conventional crop (**Fig. 2**), although the field EIQ/ha value for the GM HT crop was lower than the field EIQ/ha value for the conventional crop (in other words the GM HT crop provided an environmental improvement relative to the conventional alternative: **Fig. 3**).

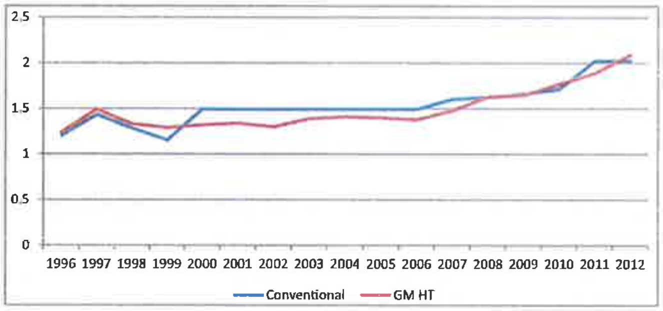

Figure 2. Herbicide active ingredient usage on GM HT and conventional soybeans in the US 1996–2012 (kg/ha).Source: derived from USDA NASS, GfK, Sankala and Blumenthal (2006[8]), Johnson and Strom (2008[9]) and representative conventional usage updated for 2009–2012 by the author Notes:
1. GM HT based on recorded usage.
2. Conventional – as recorded to 1999 when GM HT share of crop rose to over 50% of total, thereafter based on extension service/advisors assessments of representative usage levels to deliver equal levels of weed control as obtained in the GM HT crop.

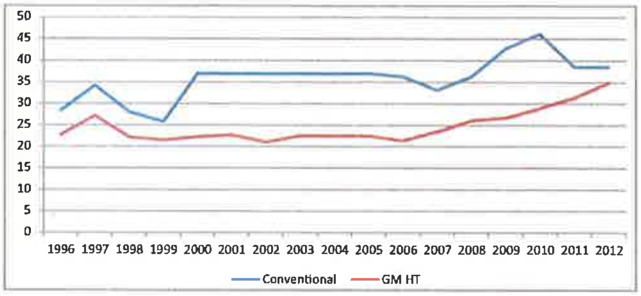

Figure 3. Herbicide usage environmental impact on GM HT and conventional soybeans in the US 1996–2012 (field eiq/ha).Source: derived from USDA NASS, GfK, Sankala and Blumenthal (2006[8]), Johnson and Strom (2008[9]) and representative conventional usage updated for 2009–2012 by the author Notes:
1. GM HT based on recorded usage.
2. Conventional – as recorded to 1999 when GM HT share of crop rose to over 50% of total, thereafter based on extension service/advisors assessments of representative usage levels to deliver equal levels of weed control as obtained in the GM HT crop.

Looking at the usage of herbicides on both the GM HT and conventional crop over the 1996–2012 period, the average amount of active ingredient (ai) used on GM HT soybeans has generally been similar to the average amount used on the conventional crop (**Fig. 2**) while the environmental load, as measured by the EIQ indicator, of GM HT soybeans has been consistently lower (and therefore better for the environment) than the conventional alternative (**Fig. 3**).

In terms of the average amount of herbicide used, in recent years this has increased on both the GM HT and conventional crops. In 2012, 59% of the GM HT soybean crop area received an additional herbicide treatment of one of the following active ingredients (the 4 most used herbicide active ingredients on soybeans after glyphosate (source: derived from GfK): 2,4-D (used pre crop planting), chlorimuron, flumioxazin and fomesafen (each used primarily after crop planting). This compares with 14% of the GM HT soybean crop receiving a treatment of one of these 4 herbicide active ingredients in 2006. As a result, the average amount of herbicide active ingredient applied to the GM HT soybean crop in the US (per hectare) increased by about 55% over this period. The increase in non-glyphosate herbicide use is in line with public and private sector weed scientist recommendations to diversify weed management programmes and not to rely on a single herbicide mode of action for total weed management. It is interesting to note that in 2012, glyphosate accounted for about the same share of total active ingredient use on the GM HT crop (about 80%) as in 1998, highlighting that farmers continue to realize value in using glyphosate because of

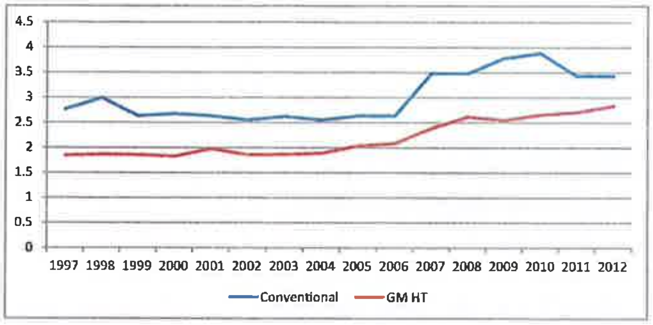

Figure 4. Herbicide active ingredient usage on GM HT and conventional corn in the US 1997–2012 (kg/ha).Source: derived from USDA NASS, GfK Kynetec, Sankala and Blumenthal (2006[8]), Johnson and Strom (2008[9]) and representative conventional usage updated for 2009–2012 by the author Notes:
1. GM HT derived from Gfk Kynetec and USDA NASS.
2. Conventional – as recorded to 2007 when GM HT share of crop rose to over 50% of total, thereafter based on extension service/advisors assessments of representative usage levels to deliver equal levels of weed control as obtained in the GM HT crop.

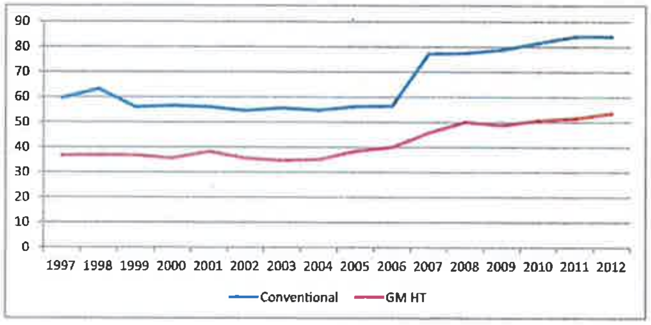

Figure 5. Herbicide usage environmental impact on GM HT and conventional corn in the US 1997–2012 (field eiq/ha).Source: derived from USDA NASS, GfK, Sankala and Blumenthal (2006[8]), Johnson and Strom (2008[9]) and representative conventional usage updated for 2009–2012 by the author Notes:
1. GM HT derived from Gfk and USDA NASS.
2. Conventional – as recorded to 2007 when GM HT share of crop rose to over 50% of total, thereafter based on extension service/advisors assessments of representative usage levels to deliver equal levels of weed control as obtained in the GM HT crop.

its broad spectrum activity in addition to using other herbicides. Adoption of weed scientist recommendations for herbicide use in conventional soybean crops has also resulted in an upward trend in herbicide usage. This increase in usage also reflects a more integrated approach to weed management aimed at minimising the chances of weed species developing resistance to (all) herbicides used in conventional soybean crops. It is also interesting to note that even on the small conventional crop, the average amount of herbicide active ingredient applied in the 2006–2012 period followed an upward trend in usage (by 78%).

GM HT maize

When GM HT technology was first used with the US corn crop, the main weed control practices were based on use of glyphosate, as a burn down tool where reduced/no tillage production systems were used plus an 'in-crop' application either before or after crop emergence. In addition, herbicides commonly used with conventional corn, notably atrazine and acetochlor, continued to be used, albeit at reduced dose rates compared to usage rates in conventional corn. As a result, the recorded average herbicide ai/ha used on the GM HT corn crop was about 0.6 to 0.7 kg/ha lower than the recorded average usage on the conventional crop in the earlier years of GM HT technology usage (**Fig.** 4). The environmental load, as measured by the EIQ indicator has also been consistently about 30% lower on the GM HT crop relative to the conventional crop (**Fig.** 5).

Over the period 1996–2012, the average herbicide active ingredient use on conventional corn has been consistently higher than usage on GM HT corn (**Fig.** 4). The associated environmental load, as measured by the EIQ indicator has also been worse for conventional corn when compared to GM HT corn (**Fig.** 5).

The average amount of herbicide active ingredient applied to both the GM HT crop and the conventional crop has increased since about 2005. These changes in herbicide usage practice on the GM HT corn crop mirror those in the soybean crop, with farmers increasingly adopting integrated weed control practices (in which farmers use a number of herbicides rather than relying on one or 2 active ingredients) in order to reduce the risk of weed resistance developing.

Since 2006, the changes in active ingredient use on the GM HT corn crop show an increasing proportion of the GM HT crop receiving additional treatments with herbicides including acetochlor, atrazine, 2 4,D, mesotione and S metolachlor, as well as use of new chemistry such as tembutrione as recommended by public and private sector weed scientists.

GM HT cotton

In the early years of adoption, weed control in GM HT cotton crops focused on the use of glyphosate post emergence (typically 2 to 3 treatments) for all users and, for some, additional use of a pre-emergence application of herbicides such as trifluralin or pendimethalin and a lay-by treatment (e.g., of prometryn or diuron). This compared with conventional cotton, where weed suppression was based on a combination of mechanical control (e.g., between crop rows) and a broader range of selective herbicide use, of which trifluaralin, pendimethalin, flumeteron, prometryn, cyanazine and MSMA were the most commonly used, typically applied in several treatments. During these early years, the recorded average herbicide ai/ha used on the GM HT cotton crop was about 2.4 to 2.5 kg/ha of herbicide active ingredient, higher than the average volume applied to the conventional crop (**Fig.** 6). In terms of the environmental load, as measured by the EIQ indicator the field EIQ/ha value for GM HT cotton was higher than the conventional crop partly because of the common use of mechanical weed control in conventional cotton being replaced by additional herbicide weed control in the GM HT crop (**Fig.** 7).

In the last 10 years, the average amount of herbicide applied to both the GM HT and conventional crop has increased. The average amount of herbicide active ingredient used on GM HT

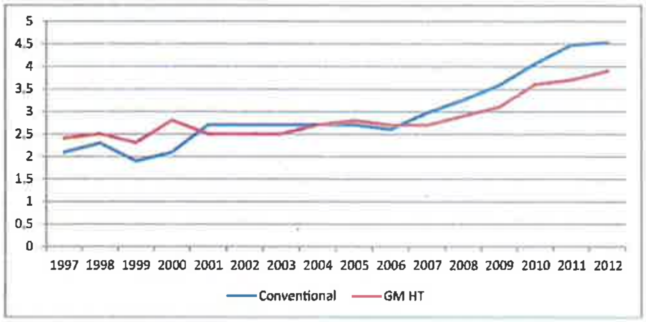

Figure 6. Herbicide active ingredient usage on GM HT and conventional cotton in the US 1997–2012 (kg/ha).Source: derived from USDA NASS, GfK, Sankala and Blumenthal (2006[8]), Johnson and Strom (2008[9]) and representative conventional usage updated for 2009–2012 by the author Notes:
1. GM HT cotton usage as recorded/derived from Gfk and USDA NASS.
2. Conventional – as recorded to 2001 when GM HT share of crop rose to over 50% of total, thereafter based on extension service/advisors assessments of representative usage levels to deliver equal levels of weed control as obtained in the GM HT crop.

cotton has increased through a combination of additional usage of glyphosate (about a 30% increase in usage per hectare) in conjunction with increasing use of other herbicides. All of the GM HT crop area planted to seed tolerant to glyphosate received treatments of glyphosate and at least one of the next 5 most used herbicides (2 4-D (pre-plant) and in-crop applications of flumoxazin, fomesafen, pendimethalin and diuron) in 2012. This compares with 2006, when only 3-quarters of the glyphosate tolerant crop received at least one treatment from the next 5 most used herbicides (2 4-D, trifluralin, pyrithiobic, pendimethalin and diuron). In other words, a quarter of the glyphosate tolerant crop used only glyphosate for weed control in 2006 compared to none of the crop relying solely on glyphosate in 2012.

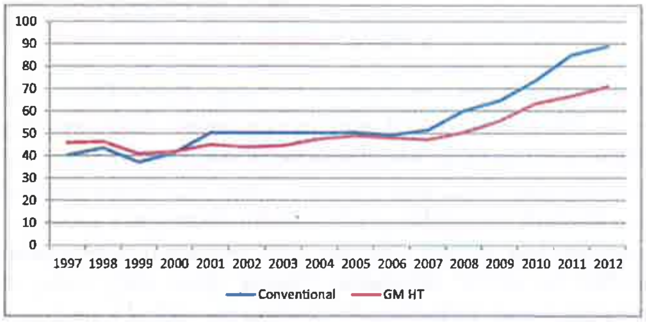

Figure 7. Herbicide usage environmental impact on GM HT and conventional cotton in the US 1997–2012 (field eiq/ha).Source: derived from USDA NASS, GfK, Sankala and Blumenthal (2006[8]), Johnson and Strom (2008[9]) and representative conventional usage updated for 2009–2012 by the author Notes:
1. GM HT cotton usage as recorded/derived from Gfk and USDA NASS.
2. Conventional – as recorded to 2001 when GM HT share of crop rose to over 50% of total, thereafter based on extension service/advisors assessments of representative usage levels to deliver equal levels of weed control as obtained in the GM HT crop.

As with herbicide usage on the soybean and corn crops, this increase in usage largely reflects changes in weed management practices in favor of a more integrated approach that aims to reduce and minimise the development of weed species becoming resistant to herbicides used. In addition, farmers have moved to using rates of glyphosate at the higher end of the weed scientists' recommended range as an additional means of mitigating the risk of resistance and providing better overall weed control performance.

Overall, since the widespread adoption of GM HT cotton, the average herbicide active ingredient use and the associated environmental load, as measured by the EIQ indicator, for conventional cotton is higher than GM HT cotton (**Fig. 6 and Fig. 7**).

GM HT (tolerant to glyphosate) sugar beet

In terms of weed control, the use of GM HT sugar beet technology has resulted in a switch in use from a number of selective herbicides to glyphosate. Before GM HT sugar beet, farmers typically used a combination of 4–6 herbicides, each at low dose rates and applied multiple times throughout the season. The GM HT treatment regime is typically 2, or possibly, 3 applications of glyphosate only.

Since the adoption of GM HT sugar beet technology, the average amount of herbicide active ingredient (per hectare) applied to the US sugar beet crop has increased by about 60% (2007–2012). Over the same period, the associated EIQ load factor (per ha) increased by about 20%. Unfortunately, there is no herbicide usage monitoring data available in the US that disaggregates usage data by type of production and therefore it is not possible to directly compare recorded usage on each of the GM HT and conventional crops. Nevertheless, based on data from industry specialists and farm surveys (e.g., Stachler J et al. (2012[10])), **Table 1** compares a typical conventional sugar beet herbicide treatment regime with the GM HT system in 2012. This confirms that the adoption of GM HT sugar beet has resulted in a significant increase in the average amount of herbicide applied to the US crop mainly because the weed management system in the conventional crop is based on low-use rates of the herbicides applied. In terms of the associated environmental load, as measured by the EIQ indicator, it also shows that the

Table 1. Typical herbicide regimes for GM HT vs conventional sugar beet: US 2012

	Active ingredient (kg/ha)	Field EIQ/ha value
Conventional		
Phenmedipham	0.17	2.78
Desmedipham	0.2	3.55
Ethofumesate	0.86	22.19
Clopyralid	0.18	3.26
Triflusulfuron	0.04	1.12
Clethodim	0.15	2.55
Total	1.57	35.44
GM HT sugar beet		
Glyphosate	2.39	36.64

Sources: based on GFK, Monsanto, Stachler J et al. (2012[10]).

Table 2. Active ingredient and field EIQ differences conventional versus GM HT canola US 1999–2012

Year	ai saving GM HT (to glyphosate: kg/ha)	ai saving GM HT (to glufosinate: kg/ha)	eiq saving GM HT (to glyphosate: field eiq/ha)	eiqsaving GM HT (to glufosinate: field eiq/ha)
1999	0.68	0.75	14.8	18.4
2000	0.68	0.75	14.8	18.4
2001	0.68	0.75	14.8	18.4
2002	0.57	0.75	17.7	18.4
2003	0.57	0.75	17.7	18.4
2004	0.79	0.83	21.2	19.8
2005	0.79	0.83	21.2	19.8
2006	0.7	0.78	19.8	18.8
2007	0.47	0.74	15.8	17.9
2008	0.47	0.74	15.8	17.9
2009	0.11	0.72	10.2	17.6
2010	0.09	0.57	9.9	14.6
2011	0.02	0.65	8.2	16.1
2012	0.06	0.57	9.4	16.6

Sources: derived from Sankala and Blumenthal (2003[4] and 2006[8]), Johnson and Strom (2008[9]), Gfk, and updates.
Note: The USDA pesticide usage survey does not include coverage of canola.

GM HT system is slightly worse, although it is important to recognize that the conventional alternative presented here relates to a typical conventional herbicide regime used and this commonly delivers an inferior level of weed control compared to the GM HT crop.

GM HT canola

Based on analysis of typical herbicide treatments for conventional, GM glyphosate tolerant and GM glufosinate tolerant canola identified in the literature[4,8,9] recorded in crop herbicide usage data and updates undertaken as part of this research, the changes in herbicide use and resulting environmental impact arising from adoption of GM HT canola in the US since 1999 are summarised in **Table 2** *and* **Table 3**. These show consistent savings in terms both of the amount of herbicide active ingredient applied and the EIQ value for both glyphosate and glufosinate tolerant canola relative to conventional canola. Since 2006, herbicide use on the GM HT canola crop has followed a similar trend to usage on other GM HT crops in that, on the advice of both public and private sector weed scientists, farmers are focusing more attention on using a more integrated approach to weed control to reduce the chances of weed resistance developing. In canola this has involved more annual switching between glyphosate and glufosinate tolerant crops and the use of additional herbicides to glyphosate and glufosinate. The main other herbicides being used (in tank mixes), especially with glufosinate, have been quizalofop and clethodim.

Table 3. Typical herbicide regimes for GM HT vs. conventional canola: US 2012

Active ingredient	Amount (kg/ha of crop)	Field EIQ/ha
Conventional canola		
Ethafluralin	1.0	23.3
Quizalofop	0.06	1.33
Clopyralid	0.05	0.91
Total	1.11	25.54
GM glyphosate tolerant canola		
Glyphosate	1.05	16.1
GM glufosinate tolerant canola		
Glufosinate	0.41	8.28
Quizalofop/clethodim	0.03/0.06	0.66/1.02
Total	0.44/0.47	8.94/9.3

Based on Johnson and Strom (2008[9]) and updated.

Analysis

A number of information sources have been used to evaluate the changes in herbicide applications for the main crops in which GM HT technology has become widely adopted over the last 17 y No one source provides all the answers to applicable impact questions and this presented a challenge. However, through use of data derived from different but complementary sources, some clear conclusions can be drawn.

Firstly, as indicated in the introduction, the use of GM HT technology in US agriculture, when compared to what can reasonably be expected if the area planted to GM HT crops reverted to conventional production methods, has resulted in a net reduction in both the amount of herbicide used and the associated environmental impact, as measured by the EIQ indicator. The technology also facilitated many farmers being able to derive the economic and environmental benefits associated with switching from a plough-based to a no tillage or conservation tillage production system.

In terms of herbicide use, the technology has contributed to a change the profile of herbicides used. A broad range of, mostly selective herbicides has been replaced by one or 2 broad-spectrum herbicides (mostly glyphosate and in some cases glufosinate) used in conjunction with one or 2 other (complementary) herbicides.

In the early years of adoption, GM HT technology resulted in aggregate reductions in both the volume of herbicides used (weight of active ingredient) and the associated environmental load, as measured by the EIQ indicator, highlighting important net environmental improvements in crops such as corn and canola. In GM HT soybeans, the average amount of herbicide active ingredient applied remained largely unaltered, while the environmental load associated with the herbicides used with GM HT soybeans fell when compared to the conventional alternative. Lastly, in GM HT cotton, the average amount of herbicide active ingredient used on GM HT cotton tended to be higher than the conventional alternative, while, as in other crops, the associated environmental load associated with herbicide use on GM HT cotton was lower than the environmental load associated with the herbicides used on the conventional alternative.

Since the mid-2000s, the average amount of herbicide applied and the associated environmental load, as measured by the EIQ indicator, have increased on both GM HT and conventional crops. A primary reason for these changes has been increasing incidence of weed species developing populations resistant to herbicides and increased awareness of the consequences of relying on a single or very limited number of herbicides for weed control.

In relation to glyphosate resistant weeds, there are currently 28 weed species recognized as exhibiting populations with resistance to glyphosate worldwide, of which several are not associated with glyphosate tolerant crops. In the US, there are currently 14 weed species recognized as exhibiting resistance to glyphosate, of which at least 2 of which are not associated with glyphosate tolerant crops (see www.weedscience.org). The first weed population with resistance to glyphosate in a crop where GM HT technology had been widely adopted was identified in 2000 and since then populations of a further 13 weed species have been identified as exhibiting resistance in crops that commonly use GM HT technology. In the US, a few of the glyphosate-resistant species, such as marestail (*Conyza canadensis*), waterhemp (*Amaranthus tuberculatus*) and palmer amaranth (*Amaranthus palmeri*) are now widespread, with the affected area being possibly within a range of 10–30% (some estimates put it higher at possibly 40%) of the total area annually devoted to corn, cotton and soybeans.

The increasing onset of weed populations showing resistance to glyphosate triggered stronger recommendations to US farmers to adopt more diversified weed control practices so as to proactively manage and minimize weed resistance (Norsworthy J et al. (2012[11]), Vencil W et al. (2012[12])). As a result, growers of GM HT crops have become much more proactive and diversified in their weed management programmes and now include other herbicides (with different and complementary modes of action) in combination with glyphosate, even where instances of weed resistance to glyphosate have not been found. This is clearly shown in the trends in herbicide use reported earlier in this paper and summarized in **Fig. 8** (examples of typical herbicide regimes used in GM HT systems are also shown in **Appendix 2**). The willingness to proactively diversity weed management systems in the GM HT crops is also influenced by a desire to maintain effective weed control and hence continue to enjoy the benefits of no tillage and conservation tillage.

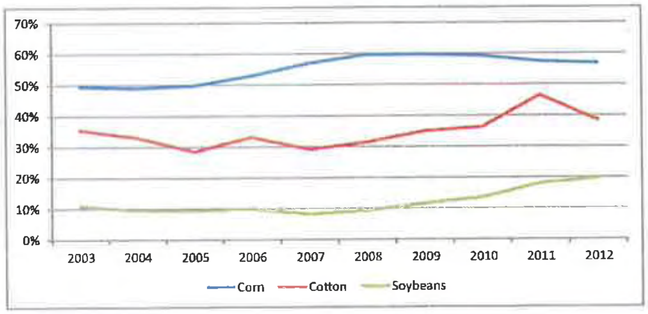

Figure 8. % of total average active ingredient used by weight with GM HT crops accounted for by non glyphosate/glufosinate herbicides 2003–2012.Source: derived from USDA NASS, Gfk.

The weed resistance development in respect of glyphosate referred to above should, nevertheless, be placed in context. Nearly all weeds have the potential to develop resistance to all herbicides: there are hundreds of resistant weed species confirmed in the International Survey of Herbicide Resistant Weeds (www.weedscience.org). Reports of herbicide resistant weeds pre-date the use of GM HT crops by decades. There are, for example, 135 weed species that are resistant to the ALS inhibitor group of herbicides and 72 weed species resistant to the photosystem II inhibitor class of herbicides. The development of weeds resistant to herbicides is therefore a problem faced by all farmers, not just those using GM HT technology. In fact, GM HT technology offered a solution to controlling some weeds that had developed resistance to mainstream herbicides used in conventional soybeans in the mid-1990s. It also offered a solution to weed resistance problems for some farmers using conventional herbicide tolerant corn crops (tolerant to ALS inhibitor herbicides). As the use of herbicides on conventional arable crops in the US is equally affected by issues of weed resistance to herbicides other than glyphosate, it is not surprising that the herbicide use patterns on conventional crops reported in this analysis have followed the same upward trends that have occurred in GM HT crops.

Overall, at the national level, in the last 6–8 y the average amount of herbicide active ingredient applied and number of herbicides used with GM HT crops has increased. In addition, during this period, the associated environmental load, as measured by the EIQ indicator, has increased. However, relative to the conventional alternative, the environmental load associated with herbicide use with GM HT crop use has continued to offer important advantages and in most cases, provides an improved environmental profile compared to the conventional alternative (as measured by the EIQ indicator). Additionally, the ability to use broad-spectrum herbicides such as glyphosate with GM HT crops has facilitated adoption and maintenance of conservation tillage systems. This fundamental change in production technique coupled with the change in profile of herbicides used with GM HT crops has resulted in, and continues to deliver, significant economic and environmental benefits to US farmers.

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Appendix 1: Typical conventional herbicide regimes required to deliver similar levels of weed control as GM HT systems 2011 and 2012

Soybeans

Conventional no tillage production systems: Mid-West

	Active ingredient (kg/ha)	Field EIQ/ha value
Option 1		
Glyphosate	1.00	15.26
2 4 D	0.66	10.05
Flumioxazin	0.07	1.78
Chlorimuron	0.02	0.4
Lactofen	0.17	6.85
Clethodim	0.11	1.83
Total	2.02	36.17
Option 2		
Glyphosate	1.00	15.26
2 4 D	0.66	10.05
Flumioxazin	0.07	1.78
Chlorimuron	0.02	0.4
Thifensulfuron	0.01	0.27
Fomesafen	0.26	6.39
Clethodim	0.11	1.83
Total	2.13	35.98
Option 3		
Glyphosate	1.00	15.26
2 4 D	0.66	10.05
Sulfentrazone	0.2	2.39
Cloransulam	0.06	0.8
Clethodim	0.11	1.83
Total	2.03	30.33

Conventional no tillage production systems: South

	Active ingredient (kg/ha)	Field EIQ/ha value
Option 1		
Glyphosate	1.00	15.26
2 4 D	0.66	10.05
Flumioxazin	0.07	1.78
Metalochlor	1.36	29.97
Fomesafen	0.30	7.32
Clethodim	0.11	1.83
Total	3.5	66.21
Option 2		
Glyphosate	1.00	15.26
2 4 D	0.66	10.05
Flumioxazin	0.07	1.78
Chlorimuron	0.02	0.4
Fomesafen	0.37	9.03
Clethodim	0.11	1.83
Total	2.23	38.35
Option 3		
Glyphosate	1.00	15.26
2 4 D	0.66	10.05
Metalochlor	1.36	29.97
Fomesafen	0.3	7.32
Aciflоren	0.26	6.21
S Metalochlor	1.45	31.88
Clethodim	0.11	1.83
Total	5.14	102.52

Conventional crop and tillage production systems: South

	Active ingredient (kg/ha)	Field EIQ/ha value
Option 1		
Flumioxazin	0.07	1.78
Metalochlor	1.19	26.14
Fomesafen	0.26	6.38
Clethodim	0.11	1.83
Total	1.63	36.13
Option 2		
Flumioxazin	0.07	1.78
Chlorimuron	0.02	0.4
Fomesafen	0.26	6.39
Clethodim	0.11	1.83
Total	0.46	10.4
Option 3		
Metalochlor	1.36	29.97
Fomesafen	0.3	7.32
Acifloren	0.26	6.21
S Metalochlor	1.45	31.88
Clethodim	0.11	1.83
Total	3.48	77.21

Weighted average all by tillage types: ai/ha 2.02 kg/ha, EIQ/ha 38.47.

Corn
Conventional no tillage production systems

	Active ingredient (kg/ha)	Field EIQ/ha value
Option 1		
Glyphosate	1.1	17.01
2 4 D	0.72	11.12
Acetochlor	1.88	37.32
Atrazine	1.45	33.21
Mesotrione	0.14	2.64
Nicosulfuron	0.02	0.48
Total	5.31	101.78
Option 2		
Glyphosate	1.1	17.01
2 4 D	0.72	11.12
Acetochlor	0.94	18.66
Clopyralid	0.1	1.83
Flumetsulam	0.03	0.56
Dicamba	0.19	4.9
Diflufenzopyr	0.04	0.69
Nicosulfuron	0.02	0.48
Total	3.14	55.54
Option 3		
Glyphosate	1.1	17.01
2 4 D	0.72	11.12
S Metalochlor	1.51	33.13
Atrazine	0.73	16.61
Mesotrione	0.14	2.64
Tembotrione	0.08	3.64
Nicosulfuron	0.02	0.48
Total	4.30	84.63

Conventional crop and tillage production systems

	Active ingredient (kg/ha)	Field EIQ/ha value
Option 1		
Acetochlor	1.88	37.32
Atrazine	1.45	33.21
Tembotrione	0.08	3.64
Nicosulfuron	0.02	0.48
Total	3.43	74.65
Option 2		
Acetochlor	0.94	18.66
Clopyralid	0.1	1.83
Flumetsulam	0.03	0.56
Mesotrione	0.14	2.64
Nicosulfuron	0.02	0.48
Total	1.23	24.17
Option 3		
S Metalochlor	1.51	33.13
Atrazine	0.73	16.61
Mesotione	0.14	2.64
Dicamba	0.19	4.9
Diflufenzopyr	0.04	0.69
Nicosulfuron	0.02	0.48
Total	2.63	58.45

Weighted average all by tillage types: ai/ha 3.43 kg/ha, EIQ/ha 84.1.

Cotton

	Active ingredient (kg/ha)	Field EIQ/ha value
South East		
Glyphosate	0.87	13.28
2 4 D	0.56	8.59
Paraquat	0.59	14.58
Fomesafen	0.29	7.07
Diuron	0.86	22.84
Pyrithiobac	0.16	3.4
Clethodim	0.13	2.15
Trifloxysulfuron	0.01	0.25
Prometryn	0.86	13.15
Trifloxysulfuron	0.01	0.24
Total	4.34	85.55
Mid South		
Glyphosate	0.87	13.28
Dicamba	0.28	7.38
Fomesafen	0.29	7.07
Paraquat	0.59	14.58
Diuron	0.86	22.84
Flumeturon	0.97	13.86
Pyrithiobac	0.16	1.4
Clethodim	0.13	2.15
Trifloxysulfuron	0.01	0.25
Prometryn	1.24	19.11
Trfloxysulfuron	0.01	0.35
Total	5.41	102.27
West Texas		
Trifluralin	0.99	18.67
Flumeteron	0.97	13.86
Pyrithiobac	0.16	3.4
Prometryn	1.24	19.11
Trifloxysulfuron	0.01	0.35
Diuron	0.86	22.84
Total	4.23	78.23

Regional weightings (based on planting area): Texas 56%, South East 25%, Mid South 19%.
Weighted average all by tillage types: ai/ha 4.48 kg/ha, EIQ/ha 85.0.

Appendix 2: Integrated weed management options: GM HT crops 2012

Soybeans

GM HT no tillage production systems: Mid West

	Active ingredient (kg/ha)
Option 1	
Glyphosate	1.00
2 4 D	0.66
Flumioxazin	0.07
Chlorimuron	0.02
Glyphosate	0.87
Lactofen (if difficult weeds resistant to glyphosate)	0.22
Total	2.62 (2.84)
Option 2	
Glyphosate	1.00
2 4 D	0.66
Flumioxazin	0.07
Chlorimuron	0.02
Thifensulfuron	0.01
Glyphosate	0.87
Fomesafen (if difficult weeds resistant to glyphosate)	0.33
Total	2.63 (2.96)
Option 3	
Glyphosate	1.00
2 4 D	0.66
Sulfentrazone	0.2
Cloransulam	0.06
Glyphosate	0.87
Cloransulam (if difficult weeds resistant to glyphosate	0.22
Total	2.93 (3.01)

GM HT no tillage production systems: South

	Active ingredient (kg/ha)
Option 1	
Glyphosate	1.00
2 4 D	0.66
Flumioxazin	0.07
Glyphosate	0.87
Metalochlor (if difficult weeds resistant to glyphosate)	1.36
Fomesafen (if difficult weeds resistant to glyphosate)	0.30
Total	2.6 (4.26)
Option 2	
Glyphosate	1.00
2 4 D	0.66
Flumioxazin	0.07
Chlorimuron	0.02
Glyphosate	0.87
Fomesafen (if difficult weeds resistant to glyphosate	0.37
Total	2.62 (2.99)
Option 3	
Glyphosate	1.00
2 4 D	0.66
Metalochlor	1.36
Fomesafen	0.3
Glyphosate	0.87
Acifloren (if difficult weeds resistant to glyphosate)	0.26
S Metalochlor (if difficult weeds resistant to glyphosate)	1.45
Total	4.19 (5.9)

GM HT conventional tillage production systems: South

	Active ingredient (kg/ha)
Option 1	
Flumioxazin	0.07
Glyphosate	0.87
Metalochlor	1.33
Glyphosate	0.87
Fomesafen (if difficult weeds resistant to glyphosate)	0.15
Total	3.14 (3.29)
Option 2	
Flumioxazin	0.07
Chlorimuron	0.02
Glyphosate	0.87
Fomesafen (if difficult weeds resistant to glyphosate)	0.26
Total	0.96 (1.22)
Option 3	
Metalochlor	1.36
Fomesafen	0.15
Glyphosate	0.87
Acifloren (if difficult weeds resistant to glyphosate)	0.26
S Metalochlor (if difficult weeds resistant to glyphosate)	1.45
Total	2.38 (4.09)

Corn

Conventional no tillage production systems

	Active ingredient (kg/ha)
Option 1	
Glyphosate	1.1
2 4 D	0.72
Acetochlor	1.88
Atrazine	1.45
Glyphosate	0.87
Mesotrione (if difficult weeds resistant to glyphosate)	0.14
Total	6.02 (6.16)
Option 2	
Glyphosate	1.1
2 4 D	0.72
Acetochlor	0.94
Clopyralid	0.1
Flumetsulam	0.03
Glyphosate	0.87
Dicamba (if difficult weeds resistant to glyphosate)	0.19
Diflufenzopyr (if difficult weeds resistant to glyphosate)	0.04
Total	3.76 (3.99)
Option 3	
Glyphosate	1.1
2 4 D	0.72
S Metalochlor	1.51
Atrazine	0.73
Mesotrione	0.14
Glyphosate	0.84
Tembotrione (if difficult weeds resistant to glyphosate)	0.08
Total	5.04 (5.12)

GM HT conventional tillage production systems

	Active ingredient (kg/ha)
Option 1	
Acetochlor	1.88
Atrazine	1.45
Glyphosate	0.87
Tembotrione (if difficult weeds resistant to glyphosate)	0.08
Total	4.2 (4.28)
Option 2	
Acetochlor	0.94
Clopyralid	0.1
Flumetsulam	0.03
Glyphosate	0.87
Mesotrione (if difficult weeds resistant to glyphosate)	0.14
Total	1.94 (2.08)
Option 3	
S Metalochlor	1.51
Atrazine	0.73
Mesotione	0.14
Glyphosate	0.87
Dicamba (if difficult weeds resistant to glyphosate)	0.19
Diflufenzopyr (if difficult weeds resistant to glyphosate)	0.04
Total	3.25 (3.48)

GM HT cotton

	Active ingredient (kg/ha)
South East	
Glyphosate	0.87
2 4 D	0.56
Paraquat (if difficult weeds resistant to glyphosate)	0.59
Fomesafen	0.29
Diuron	0.86
Glyphosate	0.87
Acetochlor	1.26
Glyphosate	0.87
Acetochlor (if difficult weeds resistant to glyphosate)	1.26
Glyphosate (if difficult weeds resistant to glyphosate)	0.87
Diuron (if difficult weeds resistant to glyphosate)	1.12
Total	6.17 (9.42)
Mid South	
Glyphosate	0.87
Dicamba	0.28
Paraquat (if difficult weeds resistant to glyphosate)	0.59
Flumeturon	0.07
Glyphosate	0.87
Acetochlor	1.26
Glyphosate	0.87
Acetochlor (if difficult weeds resistant to glyphosate)	1.26
Glyphosate (if difficult weeds resistant to glyphosate)	0.87
Diuron (if difficult weeds resistant to glyphosate)	1.12
Total	4.81 (8.06)
West Texas	
Trifluralin	0.99
Glyphosate	0.87
Trifloxysulfuron	0.01
Glyphosate	0.87
Glyphosate (If difficult weeds resistant to glyphosate)	0.87
Diuron (if difficult weeds resistant to glyphosate)	0.86
Total	2.74 (4.47)

cultivar and reduce the use of harmful chemicals, European farmers must rely on the continued use of fungicides that are far from environmentally friendly. Ironically, this choice obstructs further expansion of organically produced potatoes and tomatoes because adopting the GM Fortuna cultivar in 'conventional' agriculture could have led to reduced disease pressures benefitting alternative farming systems.

Second, Europe is the leading potato-consuming continent on a per capita basis. Most likely the continent will now become increasingly dependent on the import of potatoes from other continents, as the chemical warfare against *P. infestans* inevitably becomes less successful in Europe. These imported potatoes are likely to be GM Fortuna, anyway, so Europe is still left with the problem of tackling political resistance against it or any other GM crop.

Last but not least, Europe will again suffer from brain drain. The closure of the European plant science research unit of BASF is not only in itself a drain of qualified research environments and staff; it is yet another case where the message is conveyed to young scientists that a career in plant biotech is not a feasible choice. The question is when will European politicians gain the courage required to back up their words of promoting a science-based economy?

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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Transgenic insect resistance traits increase corn yield and yield stability

To the Editor:

'Triple-stack' corn hybrids containing genetically engineered traits conferring resistance to major lepidopteran and coleopteran insect pests and to the herbicide glyphosate (Roundup; Monsanto, St. Louis, MO) were planted on 17.8 million ha, approximately half of US corn fields in 2010. The ability of these hybrids to resist insect damage is well documented[1–3] and farmer surveys report improved farm yields[4]. However, field experiments have reported variable yield effects. Large[5,6], moderate[2] and little change in yield[7,8] have been reported across years and locations, reflecting variable feeding damage as insect populations shift and interactions between feeding damage and weather[9–11]. Commercial corn breeding programs, which measure yield on millions of plots per year, provide a unique opportunity to observe yield effects over multiple years and locations. In experiments spanning five years and the US corn belt, transgenic insect-resistance traits improved average yield and yield stability, with trait effects increasing as control yield decreases. We estimate that adoption of transgenic seeds increased corn supply in the US by 8.4 million tonnes in 2010.

Commercially successful hybrids are used as controls in corn breeding programs, allowing new hybrids to be compared with known benchmarks. Searching records from Monsanto's (St. Louis) US corn testing program, we identified nine successful corn hybrids where isogenic pairs, pairs of hybrids differing genetically only in the transgenic loci they contained, were included in >100 yield tests each, between 2005 and 2009. Trait effect—the yield effect caused by the insect-resistance traits—is the difference in yield between the triple-stacked hybrid expressing three transgenic traits and its isogenic control hybrid. Triple-stack corn hybrids express insecticidal proteins active against corn borers (CB; *Bacillus thuringiensis* (*Bt*) Cry1Ab or Cry1A.105 and Cry2Ab2), corn rootworms (CRW; *Bt* Cry3Bb1) and 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) from *Agrobacterium sp.* CP4, which confers tolerance to the herbicide Roundup (Roundup Ready [RR] corn; Monsanto, St. Louis, MO). Control hybrids contain only the RR trait.

The most widely tested corn hybrid, NB6016, had triple-stacked (NB6016 CB/CRW/RR) and RR (NB6016 RR) pairs grown together in 736 yield tests. Across all of those tests, triple-stacked NB6106 was higher yielding than the isogenic RR control in 77% of the tests, with an average yield advantage of 0.55 ± 0.81 tonnes/ha ($P = 5.3 \times 10^{-63}$, paired two-tailed *t*-test). Results for the other eight hybrids were similar (**Table 1**), with trait effect ranging from 0.27 to 1.19 tonnes/ha across locations, years and hybrids. Averaged across the nine hybrids, the triple-stacked hybrids yielded more than their isogenic RR controls by 0.51 ± 0.95 tonnes/ha. These nine hybrids were widely grown by farmers, with sales figures suggesting they were planted on about 14.7 million ha between 2005 and 2009.

Annual fluctuations in insect infestation, as well as interactions among insect damage, weather and farm management decisions, likely explain the wide range of corn yield results that the scientific literature attributes to transgenic insect-resistance traits. Insect populations exhibit large annual variations in their distribution, in their abundance and in the damage they inflict on corn[11,12]. The main lepidopteran pest of US corn, European corn borer (*Ostrinia nubilalis*), can have two and sometimes three generations per year, with each brood exerting different impacts on yield depending on infestation levels and the developmental stage of the plant when infestation occurs. Weather affects both insect populations and corn development; it can magnify or mitigate the impact of insect damage to leaves or stalks[9,13–15]. Similarly, yield losses due to corn rootworms (*Diabrotica* sp.), the most damaging coleopteran insect pests of US corn, are also quite variable and often increase as other environmental stresses accumulate[10,16–18].

Yield stability is a measure of how strongly plants are influenced by their environment. More stable varieties are less responsive to variable environmental factors and produce more consistent yields[19,20]. Because they reduce the impact of a significant environmental variable, transgenic insect-resistance traits are expected to improve yield stability. This can be tested by plotting the yield of a triple-stacked hybrid against the yield of its isogenic control across locations, where a slope of 1.0 would indicate no consistent differences in yield response across environments. Regression of triple-stacked NB6106

Table 1 Trait effect and yield stability in isogenic corn hybrid pairs grown in strip trials

Hybrid	RM[a] (days)	Observations (*n*)	Trait effect[b] (tonnes/ha)	Trait effect s.d. (tonnes/ha)	Yield stability[c]
NC4702	94	377	0.31	0.78	0.87**
EXP151	101	218	0.41	0.91	0.89**
NC5209	102	315	0.38	0.71	0.94*
NC5902	108	148	0.55	0.85	0.97
EXP260B	110	124	1.19	1.67	0.74**
NB6106	111	736	0.55	0.81	0.94**
NC6214	111	167	0.45	0.95	0.91*
EXP261	113	221	0.48	1.03	0.88**
NC6315	113	161	0.27	0.87	0.94**
Average		274	0.51	0.95	0.90

Isogenic pairs of triple-stacked (CB/CRW/RR) and control (RR) corn hybrids were tested for yield in strip trials between 2005 and 2009. Strip trials are commercial farm-based experiments where individual hybrids are planted in adjacent 'strips' running the length of the field, with width determined by locally available planting and harvesting equipment. Average strip size is approximately 0.25 to 0.5 ha. Agronomic practices used on the rest of the farm are typically used in strip trials.

[a]Relative Maturity (RM) is an indication of the length of growing season a hybrid is adapted to. [b]Trait effect, the difference in yield between isogenic pairs at each location, was tested for difference from zero using a two tailed *t*-test ($P < 0.0001$ for all examples). [c]Yield stability, the slope of a regression of triple-stacked versus control yield was tested for difference from one using a test for parallel slopes. **, $P < 0.0001$; *, $P < 0.001$.

yield against its isogenic control yield produces a slope of 0.94 ($R^2 = 0.89$), significantly <1.0 based on a test for parallel slopes ($P < 0.001$), demonstrating an increase in yield stability for the triple-stacked hybrid relative to the control hybrid. Similar results were observed with seven of the eight other isogenic hybrid pairs. Further discussion of yield stability and a principal component–based description of yield stability can be found in the **Supplementary Methods**, **Supplementary Figure 1** and **Supplementary Tables 1** and **2**. The improvement in yield stability can also be seen when trait effect is plotted against control yield (**Fig. 1**). In favorable environments, where control yield is high, the insect-resistance traits have little effect on yield. However, as control yields decline, trait effect increases, presumably due to a reduction in stresses associated with insect feeding.

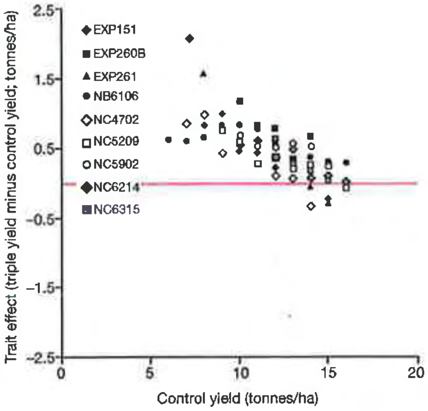

Figure 1 Yield stability in isogenic corn hybrid pairs grown in strip trials. Isogenic pairs of triple-stacked (CB/CRW/RR) and control (RR) corn hybrids were tested for yield in strip trials (**Table 1**) between 2005 and 2009. Trait effect was averaged within control yield 'bins' of 1 tonne/ha and plotted against control yield. Trait effect increases as control yield decreases. This differential response to common environments is an indication of improved yield stability.

Effects of the stacked insect-resistance traits on yield distributions were examined in more detail using a large collection of nonisogenic hybrid comparisons. Yield tests performed between 2005 and 2009 in the United States were screened to identify tests in which pairs of commercially available triple-stacked and RR hybrids were tested in the same field experiment. A total of 65,652 paired triple-stacked and control yield observations were identified. After controlling for relative maturity and product age, both of which effect yield potential, 22,163 pairs remained for analysis. Hybrids with relative maturity between 108 and 113 days made up the bulk of the data, with 15,216 paired observations. This 'RM108 to RM113 data set' included 23 unique triple-stacked hybrid backgrounds and 27 unique control hybrid backgrounds. Average annual control yield ranged from 11.4 to 13.0 tonnes/ha with an overall average of 12.1 ± 2.4 tonnes/ha. Typical of crop yield trials, which are planted on the most uniform fields available, this is 24–29% higher than yield averages reported by the US Department of Agriculture for the corresponding Crop Reporting Districts (CRDs). Variability was greater in the RM108 to RM113 data set than within the isogenic comparisons, but overall results were similar to the nine isogenic hybrids with an average trait effect of 0.42 ± 1.1 tonnes/ha ($P < 1 \times 10^{-99}$) and yield stability statistic of 0.90 ($R^2 = 0.80$). Also similar to the results from isogenic hybrids, average trait effect decreased as control yields increased. Average trait effect was 0.8 ± 1.3 tonnes/ha ($P = 3.6 \times 10^{-19}$) when control yield was within 0.25 tonnes/ha of 8 tonnes/ha (10% yield increase). This dropped to 0.7 ± 1.2 ($P = 2.1 \times 10^{-40}$), 0.6 ± 1.0 ($P = 6.9 \times 10^{-78}$) and 0.2 ± 0.9 ($P = 2.0 \times 10^{-10}$) tonnes/ha at control yields of 10 (7% yield increase), 12 (5% yield increase) and 14 (1% yield increase) tonnes/ha. These observations demonstrate that average trait effect is a function of yield distributions and not simple yield averages.

Reduction of insect feeding damage alters corn yield distributions. Yield frequency and probability distributions for triple-stacked hybrids are shifted toward higher values relative to control hybrids in the RM108 to RM113 data set (**Fig. 2a**). Yield distributions for both the triple-stacked and control hybrids are negatively skewed, typical for corn grown in the United States. Under favorable growing conditions, yields tend to cluster near the yield potential offered by the crop's genetics and agronomic system. However, a host of environmental factors, such as adverse weather, low fertility, pest or disease pressure, can act individually and synergistically to reduce yield and add a tail of lower yields to corn yield distributions. By protecting hybrids from insect damage, transgenic insect-resistance traits reduce the incidence of lower yields and shift yield distributions toward higher values, reducing production risk. As is often the case for crop yield distributions, parametric methods could not be used to describe this field level data[21]. However, the distributions could be fitted with a nonparametric kernel function[22]. Comparison of yield distributions with the two-sample Kolmogorov-Smirnov test showed that they are significantly different (K-S test statistic 0.0975, $P < 0.0001$). In this data set, corn protected from European corn borer and corn rootworm damage by the expression of *Bt* proteins was higher yielding than unprotected hybrids 67% of the time (**Fig. 1**). Anecdotal reports of large yield effects in triple-stacked corn hybrids are common, often occurring in areas where insect damage and environmental stresses such as drought coincide. Yield advantages >1.5 tonnes/ha were seen in 13% of the observations in this across-hybrid data set; thus, this study lends credence to occasional anecdotal reports of large trait effects. In recognition of the reduced production risk provided by triple-stacked hybrids, the US Department of Agriculture's Risk Management Agency offered a reduction in crop insurance

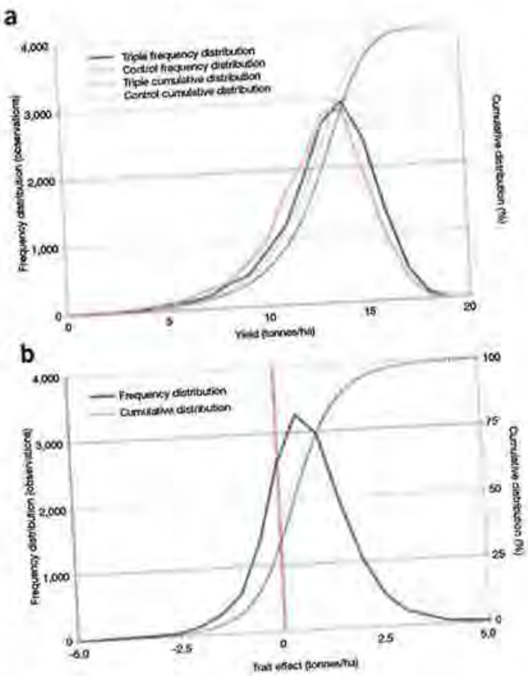

Figure 2 Distributions of grain yield and trait effect. Control (RR) and triple-stacked (CB/CRW/RR) hybrids grown in common strip trial yield tests between 2005 and 2009 are compared for grain yield. Comparisons were limited to hybrids within 2 days of relative maturity, 3 years of first commercial sales of one another, and RM108 to RM113 (15,216 observations). **(a)** Frequency and cumulative distributions of triple-stacked and control (RR) corn grain yield. Triple-stacked hybrids have a greater probability of higher yields than control hybrids. **(b)** Frequency distribution of trait effect (triple-stacked yield minus control yield). Triple-stacked yields exceed control yields 67% of the time.

premiums in 2008–2011 for farmers using corn hybrids containing the insect-resistance traits.

Farmer adoption of these *Bt* insect-resistance traits has followed a pattern similar to farmer adoption of hybrid corn technology[23], where farmers benefiting the most from the technology adopted it most rapidly. Yield loses due to insect feeding vary across the corn belt; greater losses are reported in areas with high corn rootworm and corn borer pressure[24] and, in some regions, losses are mitigated by irrigation. Insect populations were not measured in these studies. However, measured trait effects can be used to build a map indicative of economic losses caused by insect pests. The largest trait effects, reported as the percentage of times the triple stacked had a greater yield than the RR control in across-hybrid comparisons (percent wins), were observed in Illinois, Iowa, Indiana and Minnesota (**Fig. 3a**). Analysis of triple-stacked sales data for 2009 shows that farmers in CRDs with greater average trait effect purchased more triple-stacked seed than those in CRDs with lower average trait effects (**Fig. 3b**). In CRDs where triple-stacked hybrids were >50% of sales ($n = 27$), triple-stacked hybrids were higher yielding than control hybrids 69% of the time. This dropped to 61% in CRDs where triple-stacked hybrids comprised <50% of sales ($n = 22$). The correlation between trait effect and sales suggests that farmers, making independent purchasing decisions, perceive a value in the *Bt* insect-resistance traits consistent with that observed in the commercial yield tests.

Increased average crop yield is a major benefit farmers receive from the use of *Bt* transgenic insect-resistant crops. The magnitude of this benefit depends upon local environments, management practices and crop genetics, all of which contribute to local crop yield distributions. Recognizing the need to provide a simple metric to facilitate discussions on the benefits of transgenic insect-resistance traits, we suggest that the average yield benefit of 0.51 ± 0.95 tonne/ha observed for isogenic hybrid pairs is a useful description of trait effect across the US corn belt from 2005 to 2009. This value may underestimate trait effects seen in commercial production fields, as average yield levels in crop yield tests, which are planted on the most uniform fields available, are higher than county or state yield averages[25]. Even so, it is a useful approximation supported by empirical data. Using this approximation, we estimate that the adoption of *Bt* traits enabled farmers to harvest an additional 8.4 million tonnes of corn from the 16.5 million ha of triple-stacked hybrids harvested in the United States in 2010, equivalent to the creation of about 875,000 ha of new crop land.

By reducing damage caused by insects, the insect-resistance traits increase average yields and decrease 'yield gaps', differences between yields seen in farmer's fields and the yield potential of the crops genetics, environment and management system. Because trait effect increases as control yield decreases, yield benefits from insect-resistance traits can be of most importance in developing countries where lower average yields and large yield gaps occur most frequently. This has been demonstrated both in detailed studies of transgenic insect-resistant cotton[26,27] and many other farmer surveys in developing countries[4]. Reducing yield gaps, particularly in developing countries where they can be quite large, has been suggested to be the most effective method of improving both food production and environmental quality[25].

Several benefits other than yield improvements have been ascribed to the insect-resistance traits, including a reduction in pesticide usage[28], improvements in grain quality[29] and protection of neighboring crops by suppression of pest populations[30]. Crop yield increases have also been suggested to limit environmental impacts by minimizing the agricultural area needed to meet global demand for feed and fiber[31]. The importance of the economic and environmental benefits of these insect-resistance traits emphasizes the need for continued stewardship to minimize the risk that target insects will develop resistance to these beneficial genetically engineered traits.

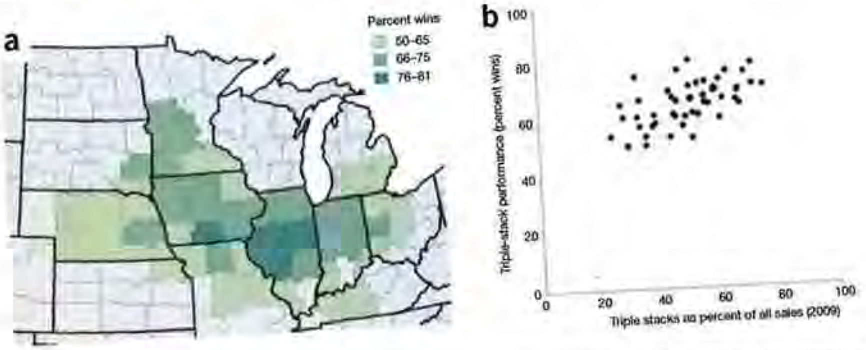

Figure 3 Geographic distribution of trait effect and technology adoption. **(a)** Trait effect, expressed as the percent of observations where the insect-resistant, triple-stacked variety had a higher yield than the RR control (percent wins), viewed by CRD. **(b)** Trait effect versus farmer adoption of triple-stacked varieties. Triple-stacked varieties make up a larger percent of sales in areas with greater trait effects. Trait effect observations ($n = 18,623$) are from the across-hybrid analysis and limited to CRDs with at least 100 observations between 2005 and 2009. Corn sales data includes sales of all commercial triple-stacked products sold in 2009.

Note: Supplementary information is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS
M.D.E. designed the analysis framework, analyzed data and wrote the manuscript. J.F., P.D., Z.L., S.M., A.R. and S.B.S. contributed to statistical analysis. T.G., J.A. and M.C. retrieved and curated data. J.F., J.R.A., C.D.P., S.B.S. and A.R. assisted in manuscript development, analytical approach and data interpretation.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details are available in the online version of the paper.

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Widespread adoption of Bt cotton and insecticide decrease promotes biocontrol services

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Over the past 16 years, vast plantings of transgenic crops producing insecticidal proteins from the bacterium *Bacillus thuringiensis* (Bt) have helped to control several major insect pests[1–5] and reduce the need for insecticide sprays[1,5,6]. Because broad-spectrum insecticides kill arthropod natural enemies that provide biological control of pests, the decrease in use of insecticide sprays associated with Bt crops could enhance biocontrol services[7–12]. However, this hypothesis has not been tested in terms of long-term landscape-level impacts[10]. On the basis of data from 1990 to 2010 at 36 sites in six provinces of northern China, we show here a marked increase in abundance of three types of generalist arthropod predators (ladybirds, lacewings and spiders) and a decreased abundance of aphid pests associated with widespread adoption of Bt cotton and reduced insecticide sprays in this crop. We also found evidence that the predators might provide additional biocontrol services spilling over from Bt cotton fields onto neighbouring crops (maize, peanut and soybean). Our work extends results from general studies evaluating ecological effects of Bt crops[1–4,6,12,13] by demonstrating that such crops can promote biocontrol services in agricultural landscapes.

Biological control is a valuable ecosystem service[14,15], but increasingly intensive farming strongly influences the populations of natural enemies and the biocontrol services they provide[16–18]. However, landscape biodiversity management and restricted use of pesticides may enhance biocontrol services in agro-ecosystems and could thus favour the development of sustainable farming[7–9]. Genetically engineered crops that express δ-endotoxins (Cry proteins) from *Bacillus thuringiensis* (Bt) have been increasingly implemented by farmers in many countries since 1996, and more than 6.6×10^7 ha of Bt crops were planted worldwide in 2011 (ref. 19). Bt crops have successfully controlled several major insect pests[1,2,4,5] and led to a drastic decrease in insecticide use on these crops[1,5,6]. Because insecticide applications have been gradually reduced in Bt crops, their widespread adoption may benefit natural enemies and may therefore potentially enhance associated ecosystem services such as the control of arthropod pests[10–12]. This last point has not yet been documented, especially with regard to the long-term landscape-level impacts[10].

From the 1970s, insecticides were applied extensively to control cotton bollworm (CBW), *Helicoverpa armigera*, the most serious insect pest on conventional cotton in China. However, control became almost impossible in the early 1990s because the pest became resistant to most insecticides, and unprecedented outbreaks in 1992 led to a wide overuse of insecticides. Consequently, in 1993, the Chinese government requested systematic insecticide applications in wheat crops for the control of the first-generation CBW; that is, before the following generations colonized cotton crops[20]. Although insecticide use decreased in cotton, this measure was not sustainable because insecticide applications were increased on wheat crops, resulting in both higher costs and environmental pollution. Bt cotton was therefore approved in 1997 for commercial use to control CBW, and it became the Chinese government's key measure against this cotton pest. It was rapidly planted on a large scale, rising to 2.4×10^6 ha by 2011 (more than 95% of the cotton crop in northern China). It managed CBW effectively, which led to decreased insecticide use on this pest[3,21].

The widespread adoption of Bt cotton may have favoured an increase in generalist natural enemy populations and promoted their associated biocontrol services. We therefore performed two assessments: first, whether implementing Bt cotton on a large scale induced an increase in populations of three groups of key generalist predators in China (ladybirds, lacewings and spiders) in both Bt cotton and three common neighbouring crops, namely maize, peanut and soybean; and second, whether this trend resulted in increased biocontrol services in agricultural landscapes in China. Aphids were selected as a pest model because they are common prey for generalist predators. During 1990–2011, research was conducted in six major cotton-growing provinces (Henan, Hebei, Shandong, Shanxi, Anhui and Jiangsu) in northern China, where about 2.6×10^6 ha of cotton and 3.3×10^7 ha of other crops (notably maize, peanut and soybean) are cultivated annually by more than ten million small-scale farmers.

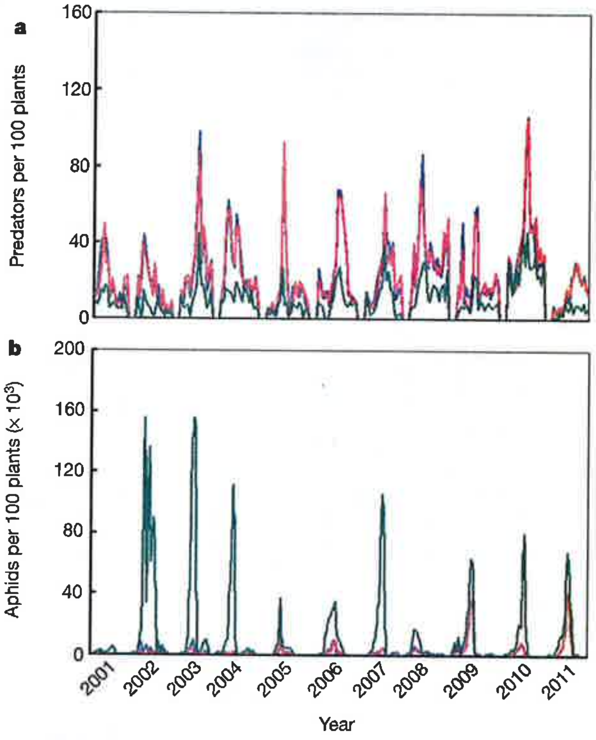

Figure 1 | Population densities of predators and aphids on cotton with different management regimes at Langfang experimental station (2001–2011). **a**, Predators. **b**, Aphids. The blue and red lines indicate Bt cotton and non-Bt cotton without insecticide sprays, respectively; the green line represents non-Bt cotton with CBW insecticide sprays (chemical control).

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Predators and cotton aphids were sampled from 2001 to 2011 in Bt and non-Bt cotton plots at Langfang experimental station in Hebei province. No significant differences were found for predator ($P = 0.341$) and aphid ($P = 0.555$) abundances between Bt cotton and non-Bt cotton with similar management methods; that is, without application of insecticide (Fig. 1a, b and Supplementary Table 1a, b). However, predator abundance was significantly lower and aphid abundance was significantly higher in plots treated with insecticides for CBW management in comparison with insecticide-free plots ($P < 0.001$) (Fig. 1a, b and Supplementary Table 1a, b), although it varied over years (significant interactions between insecticide application and year). Bt cotton does not itself affect predator and aphid population levels[10,22], and generalist predators are clearly susceptible to broad-spectrum insecticides (such as synthetic pyrethroids) used against CBW. Thereafter, insecticide-induced aphid resurgence usually occurs with widespread applications of insecticides.

Predator abundance and insecticide use in cotton were monitored in 36 locations throughout northern China during 1990–2010 (Fig. 2a and Supplementary Table 2). Predator population levels gradually increased over that period, and relatively high population levels were always observed after Bt cotton was implemented in 1997 (Fig. 2b). In 14 selected locations, all three major groups of predators (ladybirds, lacewings and spiders) showed an increasing trend similar to that of the whole predator complex (Fig. 2b). Insecticide use patterns also changed greatly with Bt cotton implementation. After the introduction of Bt cotton, the number of insecticide sprays against CBW (and other insect pests in general), mainly pyrethroid and organophosphate insecticides (Supplementary Table 3), which have multiple negative effects on natural enemies[17], was lower than during the pre-Bt cotton period, namely 1990–1996 (Fig. 2c). Moreover, predator population level and number of insecticide sprays were positively and negatively related to Bt cotton planting proportions, respectively ($P < 0.001$; Supplementary Fig. 1a, b), and indicated the effect of its large-scale adoption on the predator population trend. Regression analyses showed that fewer insecticide sprays against CBW and all insect pests were correlated to a great extent with an increase in predator populations in northern China ($P < 0.001$) (Fig. 2d, e). The results were consistent in the six provinces, and insecticide use against CBW was a driving factor for predator population level in the cotton agroecosystem (all $P < 0.05$; Supplementary Table 4).

Cotton aphid abundance was surveyed in 24 locations from 1990 to 2010 (Supplementary Table 2) to assess the biocontrol services provided by generalist predators. Linear regression analyses showed that increasing generalist predator populations were correlated with decreasing aphid abundance in northern China in general ($P < 0.001$; Fig. 3a) and in all provinces except Shanxi (Supplementary Fig. 2a–e). During the three main periods studied—that is, without Bt cotton, with less than 90% and more than 90% of Bt cotton planting in the landscapes—aphid populations decreased significantly ($P < 0.001$; Fig. 3b). In addition, aphid population was negatively related to the proportion of Bt cotton planted ($P = 0.003$; Supplementary Fig. 3). Exclusion cage trials in 2010 and 2011 at Langfang and Xinxiang experimental stations (in

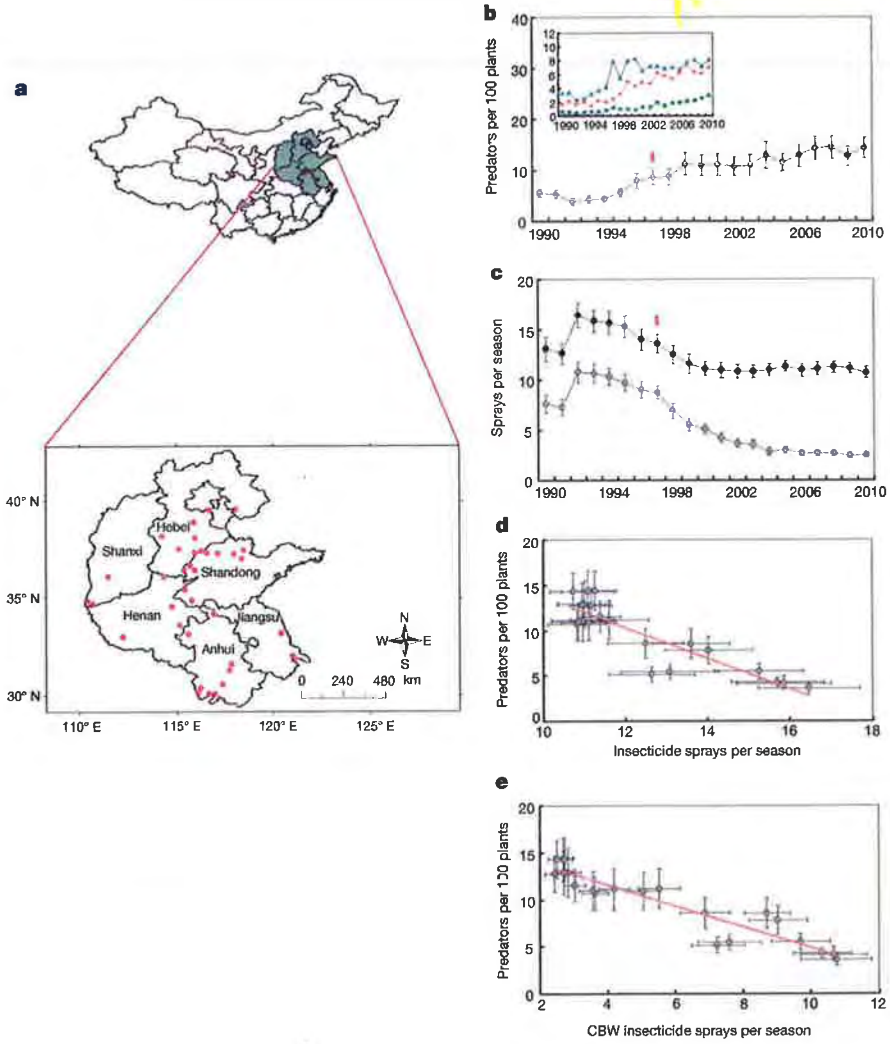

Figure 2 | Relationships between predator population density and number of insecticide sprays on cotton in northern China (1990–2010). **a**, Survey locations, indicated by red dots. **b**, Predator population density on cotton in commercial fields in 36 locations (each point represents one-year data; the red arrow indicates the beginning of Bt cotton use). Inset: population abundance of ladybirds (blue), spiders (red) and lacewings (green), collected from 14 locations. **c**, Number of insecticide sprays for CBW (grey points) and all insect pests (black points) on cotton; each point represents one-year data. **d**, Linear relationship between total number of insecticide applications, determined by pooling all treatments against all the insect pests on cotton (x), and the predator abundance (y) in cotton ($y = -1.69x + 30.63$, $F_{1,19} = 71.19$, $R^2 = 0.79$, $P < 0.0001$). **e**, Linear relationship between number of insecticide applications for CBW only (x) and predator abundance (y) ($y = -1.11x + 16.03$, $F_{1,19} = 137.32$, $R^2 = 0.88$, $P < 0.0001$). The data in **d** and **e** are replotted from **b** and **c**. All error bars show s.e.m.

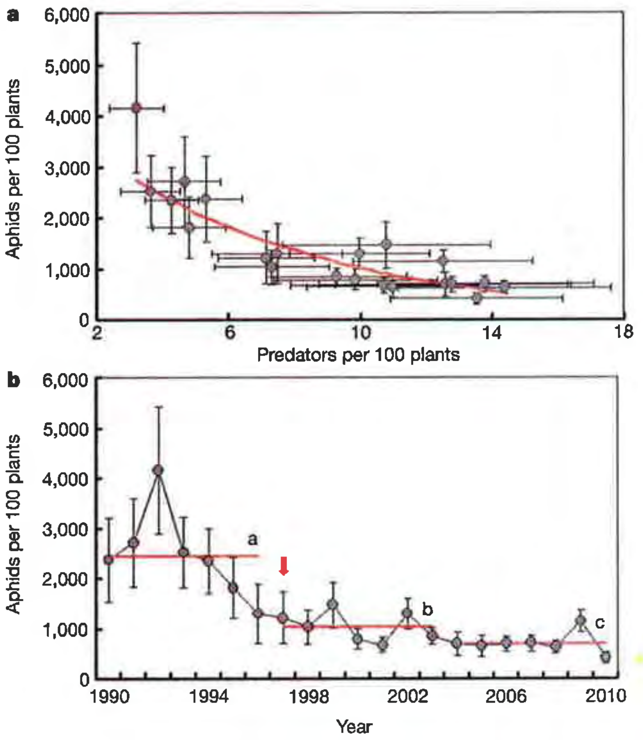

Figure 3 | Population abundance of cotton aphid in northern China (1990–2010) and relationship with predator abundance on cotton. **a**, Regression analysis between abundance of aphids (*y*) (log$_e$-transformed) and predator abundance (*x*) ($y = e^{-0.15x + 8.39}$, $F_{1,19} = 69.67$, $R^2 = 0.79$, $P < 0.0001$). **b**, Aphid population density on cotton in commercial fields in 24 locations (each point represents one-year data, and the red arrow indicates the beginning of Bt cotton use). Red lines show the mean population density of aphids in cotton fields during three main periods, namely before Bt cotton planting (1990–1996), when Bt cotton planting was less than 90% of cotton surfaces planted (1997–2003) and when it was more than 90% (2004–2010). Red lines bearing different letters are significantly different at the $P < 0.05$ level in least-significant-difference post-hoc tests (one-way analysis of variance on log$_e$-transformed data: $F_{2,18} = 27.57$, $P < 0.0001$). All error bars show s.e.m.

Hebei and Henan provinces, respectively) further demonstrated the significant effects of predators on aphid population growth in cotton fields (Supplementary Fig. 4a, b). As the cotton aphid populations declined, an invasive whitefly in cotton, *Bemisia tabaci*[20], probably served as an alternative prey for the increasing predator populations.

All these results indicate that the widespread adoption of Bt cotton ultimately promotes biocontrol services in the agroecosystem because decreased insecticide use leads to an increase in predator populations. Broadly speaking, measures that preserve predators in cotton fields greatly help to control aphid populations; for example, when insecticide applications in wheat were requested by the Chinese government (1993–1996) to prevent CBW outbreaks in cotton (see above), it led to a decreasing trend in aphid abundance (Fig. 3b).

Predator abundance was also monitored from 2001 to 2011 in three neighbouring crops: maize, peanut and soybean at Langfang experimental station. There was a positive relationship between predator abundance in cotton and soybean ($P = 0.019$; Fig. 4a), as well as between cotton and peanut (marginally significant, $P = 0.075$; Fig. 4b). We observed a similar trend in maize but it was not significant ($P = 0.216$; Fig. 4c). The increased predator abundance in maize was linked to a decrease in aphid pest abundance in that particular crop (marginally significant, $P = 0.061$; Fig. 4d).

Biocontrol services are important components in agro-ecosystems and could lead to the development of sustainable agriculture[7,15,23]. In conventional agricultural practices, insecticides are frequently used to control targeted pests, but they can lead to outbreaks of secondary pests by suppressing their natural enemies[24]. This so-called insecticide-induced resurgence was first reported for cotton aphid in the 1970s and was regarded as a key factor leading to population outbreaks of this pest in China[25]. Our work demonstrates the importance of natural enemies in the long-term suppression of the cotton aphid. The widespread adoption of Bt cotton, as a sustainable measure to reduce insecticide use, has indirectly promoted generalist predator abundance in Bt cotton fields but also to a smaller extent in three common adjacent crops in northern China. Bt crops therefore might enhance biocontrol services in agricultural landscapes through an increased abundance of generalist natural enemies. This study provides key information on long-term landscape-level ecological effects of Bt crops as well as useful insights, for example into the management of pest resurgence problems reported for many pests worldwide[26].

Generalist predators usually have great dispersal ability and can rely on various food sources. Hence, not only can they synchronously attack different insect pests in one field, but they can also colonize different habitats in different seasons[27,28]. Furthermore, some habitat management measures, such as inter-planting different crops or wild plants, have been adopted to provide resources such as food supply or shelter for natural enemies, thus increasing conservation biological control in adjacent fields[7,9,27,28]. We have demonstrated that decreasing insecticide application, through widespread Bt cotton plantings, sustained generalist predators and helped to suppress aphid populations in this

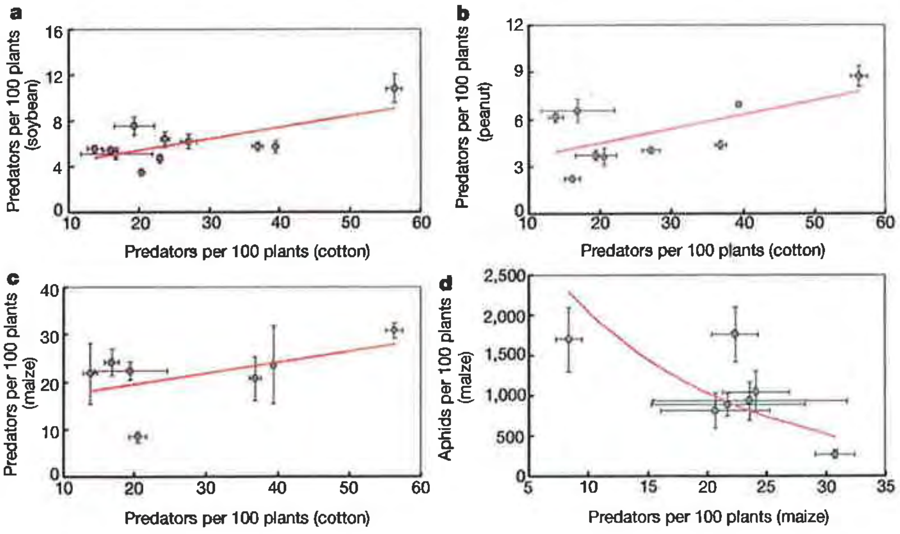

Figure 4 | Relationships between predator abundance on cotton and in three other crops, and between predator and aphid abundances in maize. Data on soybean (2001–2011), peanut (2001–2005 and 2008–2011) and maize (2001–2003 and 2008–2011) were collected at Langfang experimental station. **a**, Linear relationship between predator abundance on cotton (*x*) and on soybean (*y*) ($y = 0.10x + 3.38$, $F_{1,9} = 8.11$, $R^2 = 0.47$, $P = 0.0191$). **b**, Linear relationship between predator abundance on cotton (*x*) and on peanut (*y*) ($y = 0.09x + 2.66$, $F_{1,7} = 4.38$, $R^2 = 0.38$, $P = 0.0747$). **c**, Linear relationship between predator abundance on cotton (*x*) and on maize (*y*) ($y = 0.23x + 14.96$, $F_{1,5} = 2.00$, $R^2 = 0.29$, $P = 0.2164$). **d**, Relationship between predator abundance (*x*) and abundance of aphids in maize (*y*; log$_e$-transformed data) ($y = e^{-0.07x + 8.31}$, $F_{1,5} = 5.80$, $R^2 = 0.54$, $P = 0.0610$). All error bars show s.e.m.

crop. Large-scale insecticide reduction is the key driver in such processes (for example see the period 1993–1996, during which insecticide decrease favoured an increase in predator populations and a decline of aphid populations). Higher generalist predator population levels in Bt cotton lead to lower insect pest levels in the crop, and these predators might provide additional biocontrol services spilling over from cotton fields onto neighbouring crops, although further work should be performed to document this last point. Broadly speaking, the deployment of Bt crops may favour biocontrol services and enhance economic benefits not only in Bt crop fields but also in the whole agricultural landscape. Field studies indicated that Bt crops protected natural enemies in comparison with non-Bt crops, which rely on conventional insecticides[22,29]. Our present study, demonstrating that biocontrol services are potentially provided by Bt crops throughout the agricultural landscape, may offer new options in developing conservation biological control measures at the landscape level.

Critical concerns about the ecological risk assessment of transgenic crops still remain, especially on a large scale[29]. The present study confirms no negative effects of one Bt crop, Bt cotton, on generalist predators in agricultural landscapes in China. More particularly, we have demonstrated a marked increase in generalist predator population levels and associated biocontrol services linked to decreased insecticide use owing to the widespread adoption of the Bt crop. Our work provides a comprehensive, long-term and large-scale assessment of the possible ecological and agricultural effects of transgenic crops.

METHODS SUMMARY

The study was based on large-scale surveys of predator and cotton aphid populations in cotton fields of northern China from 1990 to 2010 and on experiments and surveys that were performed at Langfang experimental station of the Chinese Academy of Agricultural Science (CAAS) during the period 2001–2011. The surveys and experiments focused on three major generalist predator groups (ladybirds, lacewings and spiders) and on aphid pests in cotton and in three common cotton-neighbouring crops, namely maize, peanut and soybean.

At the CAAS, we first assessed how cultural practices could affect predator and aphid populations in the long term in cotton fields; cotton plots were established every year and the abundance of predators and cotton aphids was surveyed in three different plot types: Bt cotton, non-Bt cotton and non-Bt cotton with insecticide. Second, we determined the impact of predators on aphid population in cotton by means of exclusion cage trials. Third, we evaluated the impact of implementing Bt cotton on predator and aphid populations in the neighbouring crops. Field plots were established in cotton, maize, peanut and soybean, and population dynamics of predators and aphids were monitored.

Large-scale surveys were conducted in six provinces in northern China (36 locations, 10–20 fields per location) to evaluate the impact of insecticide applications on the abundance of predators and aphids in cotton fields. We tested, first, the relationship between predator abundance and insecticide use during the period 1990–2010 (that is, including the period before and during the widespread adoption of Bt cotton by farmers), and second, how cotton aphid density was related to predator abundance during the same period.

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Contributions K.W., Y.L. and Y.G. designed and performed the experiments. Y.J. performed the surveys. Y.L., K.W. and N.D. analysed the data and shared in the scoping and writing responsibilities.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at www.nature.com/nature. Correspondence and requests for materials should be addressed to K.W. (kmwu@ippcaas.cn).

METHODS

Aphid pests and predator complex considered in the study. In northern China, several aphid species are reported as pests on cotton, maize, peanut and soybean. *Aphis gossypii* Glover (cotton aphid) is the main aphid pest in cotton fields in northern China where there are two key biotypes (called seedling and summer aphids, respectively). Only the summer aphid, which colonizes fields from early July to late August, is considered a major cotton pest[20,30,31]. The seedling aphid is controlled by insecticide treatments applied on the seeds; these compounds do not last long enough within plants to provide control of the summer aphid[20]. *Rhopalosiphum maidis* Fitch, *R. padi* Linnaeus and *Sitobion avenae* Fabricius are the three dominant aphid pest species on maize[31], and *A. glycines* Matsumura and *A. craccivora* Koch are the main aphid species on soybean and peanut, respectively[31]. In our study, the above aphid species were considered in assessing the biocontrol services provided by generalist predators.

In northern China, there are three dominant groups of generalist predators in cotton field (more than 90% of all the predators[30]): ladybirds, lacewings and spiders. In our study we therefore focused on a predator complex composed of ladybirds (*Propylea japonica* Thunberg, *Harmonia axyridis* Pallas, *Coccinella septempunctata* L. and *Adonia variegata* Goeze), lacewings (*Chrysopa septempunctata* Wesmael, *Chrysoperla sinica* Tjeder and *Chrysopa formosa* Brauer) and spiders (*Erigonidium graminicolum* Sundevall, *Misumenopos tricuspidata* Fabricius and *Pardosa t-insignita* Boes. et Str.); these compose the most common predators in agricultural landscape of that region. These groups of predators are also common in maize, peanut and soybean fields and were thus also considered as a predator complex for these three crops[32–34].

Impact of agricultural practices on predator and cotton aphid populations. Survey experiments were conducted from 2001 to 2011 at Langfang experimental station (39.53° N, 116.70° E), Chinese Academy of Agricultural Sciences (CAAS), Hebei province, China. Fifteen cotton plots (400 m^2 each) were established every year and were managed with agronomic practices that are standard in northern China. A randomized block design with three replicates was used, which included two Bt and two conventional cotton varieties. One Bt cotton variety expressing *Cry1Ac* (NuCOTN33B) and another Bt cotton varieties expressing *Cry1A* (SGK321) were supplied by Monsanto Co. and the Biotechnology Research Institute, CAAS, respectively. Two conventional cotton varieties (Shiyuan321 and Zhong12) were obtained from the Institute of Plant Protection, CAAS. Shiyuan321 was the non-transgenic isoline of SGK321. Every year, the trial consisted of three treatments: Bt cotton and non-Bt cotton plots without insecticide, and non-Bt cotton (one variety, Zhong12) plots with insecticides. β-Cypermethrin (pyrethroid) and phoxim (organophosphate) were used when insecticides were applied. The choice of these two insecticides, and their frequency of application, were both based on management guidelines for CBW (*Helicoverpa armigera*) used throughout the early 1990s in northern China[20] (Supplementary Table 3).

The abundances of predators and cotton aphid were surveyed in the three cotton plot types (Bt cotton, non-Bt cotton and non-Bt cotton with insecticide) every 4 or 5 days from mid-June to late August from 2001 to 2011. At each sampling date, 100 plants at five random locations per plot[35] were visually inspected and all predators and aphids were recorded. No significant differences ($P > 0.05$) were found between cotton varieties, so we combined NuCOTN33B and SGK321 as Bt cotton, and Shiyuan321 and Zhong12 as non-Bt cotton, for further analysis. A three-way ANOVA was used to analyse the effects of the cotton variety (Bt cotton and non-Bt cotton), insecticide treatments (chemical control and non-chemical control) and sampling year on predator and aphid abundance, and the interactions between year and cotton variety, and between year and insecticide spray; the means were compared by the least-significant-difference (LSD) test at $P = 0.05$.

Survey of predators and cotton aphid in cotton crops in northern China. From 1990 until 2010, commercial cotton fields in 36 locations in six provinces (Henan, Hebei, Shandong, Shanxi, Anhui and Jiangsu) of northern China were surveyed for predators and cotton aphid (Supplementary Table 2). Insect populations were recorded every 3–10 days from early June to late August every year. For each survey, 10–20 cotton fields were sampled per location. Within each field, a total of 50–100 cotton plants at five random locations were visually inspected for predators[30]. Among the 36 locations, ladybirds, lacewings and spiders were recorded as a predator complex in 22 locations, whereas in 14 sites the three predator types were recorded individually. The 14 locations included Anxin and Xinji from Hebei province; Dezhou, Binzhou and Chengwu from Shandong province; Ruicheng, Yongji and Linfen from Shanxi province; Dongzhi, Wangjiang and Taihu from Anhui province; and Dafeng, Tongzhou and Haimen from Jiangsu province. The cotton aphid populations were surveyed in 24 locations in five provinces (Supplementary Table 2), using the same sampling schedule as for survey of predators[30]. On each plant, an upper leaf, a middle leaf and a lower leaf were examined for aphid presence. At the same time, all insecticide applications (for management of CBW and other arthropod pests) were recorded per field per year.

Linear regression analyses were used to assess the relationship between predator abundance and insecticide use on the data set gathered from 1990 to 2010—that is, including the period during which Bt cotton was increasingly adopted in China by farmers. Both simple and forward stepwise regressions were used to relate predator abundance and insecticide use against CBW and all insect pests for each province and the whole of northern China in the 1990–2010 data set. Simple linear models were used to assess the relationship between aphid density (log-transformed) and predator abundance from early July to late August (in the 1990–2010 data set) for each province and for the whole of northern China. Linear regression analyses were used to assess the relationship between predator abundance and aphid abundance (log-transformed) with Bt cotton planting proportions. In this analysis, the mean abundances of predators and aphids during 1990–1996 were included as the data when the Bt cotton planting proportion was 0.

To evaluate the impact of the predators on cotton aphid population further, exclusion cage trials were conducted in 2010 and 2011 at Langfang experimental station and Xinxiang experimental station of CAAS (Henan Province, 35.09° N, 113.48° E). This trial included a caged treatment and an open-field treatment as control[18,36]. The cage was 2 m wide by 2 m wide by 1.5 m high and made from the insect mesh net, which allowed the emigration and immigration of alate aphids and its parasitoids, but blocked the predators[37]. Ten cotton plants were covered in each cage. This trial began in July, when almost only apterous aphids were in the field[38], and was limited to 15 days to prevent the appearance of alate aphids in the cage[18,36]. At each site, cage treatments with three or four replicates were established when aphid density reached an average of 2 individuals per plant in 2010 and 20 individuals per plant in 2011. We recorded the aphid abundance 15 days after treatment. Meanwhile, predator densities were surveyed three times, on day 0, day 5 and day 10, in ten randomly selected cotton plants in open field during the whole trial. The aphid abundance in caged and open plants was compared by one-way ANOVA followed by a post-hoc LSD test. Before analysis, the data for aphid abundance were $\log_e$-transformed.

Impact of Bt cotton adoption on populations of predators in neighbouring crops. Population dynamics of the predator complex were monitored in cotton, soybean, peanut and maize field plots from 2001 to 2011 (except for maize, which was monitored during 2001–2003 and 2008–2011, and soybean, which was monitored during 2001–2006 and 2008–2011) at Langfang experimental station. Every year, a total of nine field plots (400 m^2 each) were established for each crop type and they were managed in the same way, applying the same fertilizers and irrigation treatment, free of any pesticide. A randomized block design with three replicates for each crop type was used. One Bt cotton variety, SGK321, was supplied by the Biotechnology Research Institute (CAAS); the maize (var. Shengshi29), soybean (var. Zhonghuang13) and peanut (var. Huayu16) were provided by Langfang experimental station (CAAS), the Institute of Crop Sciences (CAAS) and the Shandong Peanut Research Institute, respectively. The abundance of predators was recorded in the four different crops (Bt cotton, maize, peanut and soybean) every four or five days from mid-June to late August. At each sampling date, 100 plants in five random spots per plot were visually inspected and all predators were recorded. Linear regression analyses were used to assess the relationship between seasonal density of predators on cotton and soybean/peanut (data set covering the 2001–2011 period) and maize (data set covering the 2001–2003 and 2008–2011 periods).

For the maize plots, maize aphids were also recorded because they are well known as the main pests on maize in northern China. Population levels of aphids on soybean and peanut crops at Langfang experimental station were very low during the course of our study and therefore the data could not be considered in the framework of the study. A simple linear model was used to assess the relationship between aphid abundance (log-transformed) and predator abundance on maize.

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carbanions in the substrates as electron donors (*12*), a mechanism that is not likely in the case of a polysaccharide substrate. If the oxidation step was to happen first, this would imply that CBP21 catalyzes cofactor-independent oxygenation of a saturated carbon, which is unprecedented and perhaps not very likely. On the other hand, such a mechanism could yield an intermediate product (for example, an ester bond) that may be more prone to hydrolysis than the original glycosidic bond. Alternatively, the hydrolytic step could occur first, which would imply that CBP21 is capable of hydrolyzing glycosidic bonds in a crystalline environment using a hitherto unknown mechanism. Such a hydrolytic step would require some degree of substrate distortion (*13*, *14*), which seems challenging in a crystalline packing. However, in favor of this mechanism, the subsequent oxidation of the resulting sugar aldehyde ("reducing end") is more straightforward than oxidation of a saturated carbon. Clearly, further experiments are needed to unravel mechanistic details of the remarkable reaction catalyzed by CBP21.

CBP21 introduces chain breaks in what probably are the most inaccessible and rigid parts of crystalline polysaccharides, and its mode of action differs fundamentally from the mode of action of glycoside hydrolases. Glycoside hydrolases are designed to host a single "soluble" polysaccharide chain in their catalytic clefts, and their affinity and proximity to the crystalline substrate tend to be mediated by nonhydrolytic binding domains. In contrast, CBP21 binds to the flat, solid, well-ordered surface of crystalline material and catalyzes chain breaks by a mechanism that results in oxidation of one of the new chain ends. The chain break will result in disruption of crystalline packing and increased substrate accessibility, an effect that may be enhanced by the oxidation of the new chain end that disrupts the normal chair conformation of the sugar ring and introduces a charge.

The enzyme activity demonstrated in this study is difficult to identify because products have low solubility and potentially a high tendency to remain attached to the crystalline material. Based on the structural homology and other similarities discussed above, we propose that GH61 proteins may have the same activity as CBP21, but the even lower product solubilities and higher crystalline packing of cellulose compared with chitin (*15*) make direct detection of this activity very challenging. However, a first glimpse of the potential of GH61 proteins for cellulose conversion has been presented recently (*7*). The dependency of these enzymes on the presence of molecular oxygen and reductants provides guidelines for process design.

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Areawide Suppression of European Corn Borer with Bt Maize Reaps Savings to Non-Bt Maize Growers

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Transgenic maize engineered to express insecticidal proteins from the bacterium *Bacillus thuringiensis* (Bt) has become widely adopted in U.S. agriculture. In 2009, Bt maize was planted on more than 22.2 million hectares, constituting 63% of the U.S. crop. Using statistical analysis of per capita growth rate estimates, we found that areawide suppression of the primary pest *Ostrinia nubilalis* (European corn borer) is associated with Bt maize use. Cumulative benefits over 14 years are an estimated $3.2 billion for maize growers in Illinois, Minnesota, and Wisconsin, with more than $2.4 billion of this total accruing to non-Bt maize growers. Comparable estimates for Iowa and Nebraska are $3.6 billion in total, with $1.9 billion for non-Bt maize growers. These results affirm theoretical predictions of pest population suppression and highlight economic incentives for growers to maintain non-Bt maize refugia for sustainable insect resistance management.

During the past decade, adoption of transgenic crop technology increased worldwide to reach 134 million ha of transgenic crops planted in 25 countries during 2009 (*1*). In the United States, maize has been the most abundant transgenic crop planted to resist insect pests, with hybrids engineered to express insecticidal proteins isolated from the bacterium *Bacillus thuringiensis* [i.e., Bt maize (*1*, *2*)]. Historically, the most widespread insect pest throughout the U.S. Corn Belt has been the European corn borer, *Ostrinia nubilalis* (Hübner). The pest was accidentally introduced in the eastern United States in 1917 and subsequently spread with devastating results; losses are estimated at $1 billion per year (*3*). Given the broad host range of *O. nubilalis*, the potential for Bt maize to suppress populations regionally was unclear. Furthermore, the economic impacts of such suppression had not been considered.

In 2009, plantings of Bt maize (with traits specific to preventing damage by lepidopteran pests) reached 22.2 million ha, and for the first time exceeded 63% of the total area planted with maize in the United States (*4*). Most of the Bt maize is distributed throughout the Midwestern U.S. Corn Belt (*4*) (Fig. 1). Although "stacked" Bt events (maize varieties expressing multiple Bt toxins) directed at preventing herbivory from multiple insect pests are available (*1*, *4*), nearly all Bt maize hybrids sold in the United States express toxins that control *O. nubilalis* (*2*, *4*, *5*). Because of Bt maize's high efficacy (*6*), there is concern that insects will evolve resistance to Bt

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toxins (*5*, *7*, *8*). To delay evolution of resistance, the U.S. Environmental Protection Agency (EPA) mandated that a minimum 20 to 50% of total on-farm maize be planted as non-Bt maize within 0.8 km of Bt fields as a structured refuge for susceptible *O. nubilalis.* Use of non-Bt maize refugia is an important element of long-term insect resistance management (*9*).

Some maize producers have been skeptical of allowing *O. nubilalis* damage in non-Bt maize refugia (*10*, *11*). However, modeling (*7*, *12*) provided a theoretical rationale for how local suppression of *O. nubilalis* could occur. Suppression was supported by the hypothesis that preferential moth oviposition in early-planted Bt maize fields (*7*) would reduce larval damage in nearby late-planted non-Bt maize. More generally, for Bt and non-Bt maize fields with similar planting dates, *O. nubilalis* females are not able to distinguish between Bt and non-Bt maize for oviposition (*13*). Thus, with high larval mortality, Bt maize fields become an effective "dead-end" trap crop for *O. nubilalis* originating elsewhere (*14*). Although the models were theoretically appealing, it was not possible during early Bt maize commercialization to verify the magnitude of pest population suppression. Adult *O. nubilalis* are known to readily disperse among farms at distances of at least 800 m throughout their lifetime (*15*). Also, although maize is a major host, this pest colonizes >200 host plants including green beans, potato, and numerous weed species common to the Midwest region (*3*).

Surveys of *O. nubilalis* populations have extended from the initial documented invasion of the pest into the midwestern United States in the 1940s through the commercial adoption of Bt maize during the period 1996 to 2009. Surveys have included statewide annual fall surveys (*16*) for diapausing larvae in Minnesota, Illinois, and Wisconsin, and less extensive summer trapping for adult moths with light traps (*17*, *18*) in Illinois, Minnesota, Nebraska, and Iowa. These states have experienced a range of Bt maize adoption since 1996, including high levels in Minnesota, Nebraska, and Iowa, moderate levels in Illinois, and low levels in Wisconsin (Figs. 1 and 2) (*18*).

Historically, larval surveys have indicated that *O. nubilalis* populations have been episodic, characterized by ~6- to 8-year periodicity indicative of density-dependent population growth (*7*, *12*). Much of the population cycling has been attributed to the pathogen *Nosema pyrausta* (*12*, *19*). However, since commercialization of Bt maize, some periodicity has persisted (Fig. 2), but larval populations have declined relative to the pre-Bt era, particularly since 2002. These trends are evident in measures of larval abundance in non-Bt refuge fields alone, as well as in landscape-level means, for Bt- and non-Bt fields combined. Similar declines were found in measures of adult moth populations at eight locations in Minnesota, Illinois, Iowa, and Nebraska (*18*) (fig. S1).

To analyze the effects of Bt maize adoption on *O. nubilalis* populations, we estimated annual per capita growth rates (*20*) from fall larval surveys in non-Bt fields and analyzed them in relation to concurrent proportions of maize planted with Bt maize. Estimation also included antecedent larval densities in non-Bt fields, because *O. nubilalis* larval mortality increases with larval density (*7*, *12*) and population growth more generally depends inversely on density (*21*). Analysis used least-squares regression of growth rates in natural logarithm scale with three main effects: a state indicator variable to capture historical differences in mean densities among the three states, the natural logarithm of the antecedent larval density, and the proportion of Bt maize. Relative support for different models was evaluated with multimodel inference, with support weights based on the Bayesian information criterion, which balances reductions in residual sums of squares with numbers of parameters estimated (*18*, *22*).

Relative support was greatest (82%) for the hypothesis that per capita growth rates differed among the three states, were inversely related to larval density, and were also inversely related to level of Bt maize adoption in each state (Table 1 and Fig. 3). The model with greatest support accounted for 38% of the variation in growth rates in non-Bt fields over all states and years combined. Models with just one or two of the three main effects and with interactions among the main effects had weak support (*18*) (table S2).

We used the fitted regression models to estimate mean densities for populations before and after adoption of Bt maize in each state (Table 1). Before Bt maize was adopted, the density in Minnesota was 59 larvae per 100 plants; from 1996 onward, when

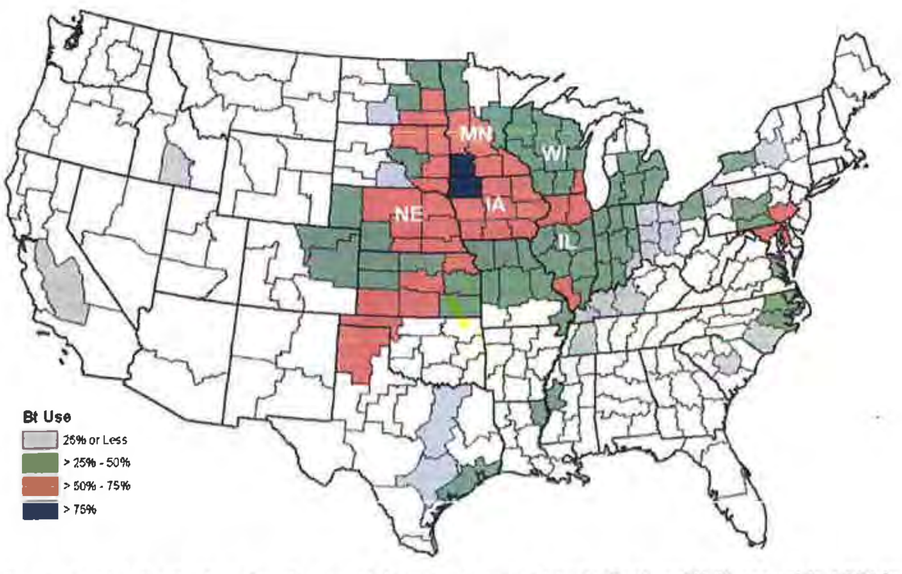

Fig. 1. Spatial distribution of maize containing one or more Bt traits for *O. nubilalis* control in 2006 in the United States. Bt maize data are from USDA crop reporting districts reporting >40,470 ha of maize, including the five states represented in this analysis (IL, Illinois; MN, Minnesota; WI, Wisconsin; IA, Iowa; NE, Nebraska). Areas in white had negligible maize hectares. Data are based on addresses of customer or retail outlet seed sales accounts, which may not accurately indicate cropping districts in which seed was ultimately planted. [©2008 Agricultural Biotechnology Stewardship Technical Committee]

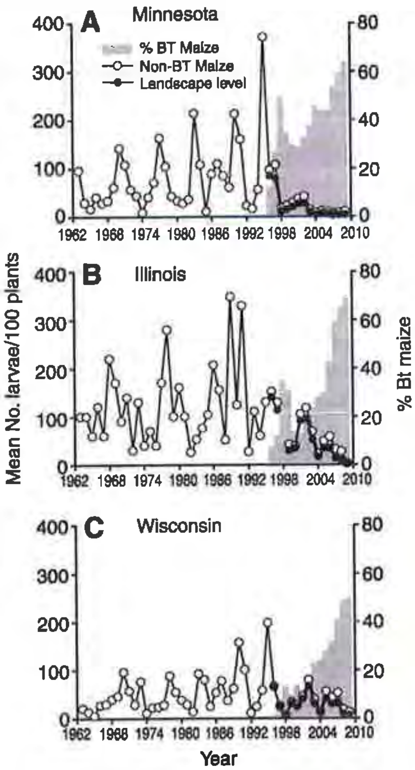

Fig. 2. Statewide average numbers of *O. nubilalis* larvae per 100 plants over the period 1963 to 2009 in (**A**) Minnesota, (**B**) Illinois, and (**C**) Wisconsin. Minnesota data were adjusted to landscape means (Bt and non-Bt maize fields) for comparisons with Illinois and Wisconsin landscape means, based on proportion of non-Bt corn hectares (*18*). Illinois and Wisconsin landscape means were adjusted for non-Bt maize hectares planted in each state (*18*).

Table 1. Regression statistics and estimated mean densities of *O. nubilalis* larvae per 100 plants before adoption of Bt maize in three midwestern states, and in non-Bt fields for 14 years (1996 to 2009) after adoption of Bt maize. Coefficients for the regression model for per capita growth rate, $r = \ln(N_t/N_{t-1})$, are b_0 for intercept, b_1 for regressor $D = \ln(N_{t-1})$, and b_2 for regressor PBt = Bt maize proportion of crop.

				Model coefficients			Pre-Bt density†		Avg.	Bt-era density	
Analysis*	State	n	R^2	b_0 (±SE)	b_1 (±SE)	b_2 (±SE)	Mean	CI	PBt	Mean	CI
By state	Minnesota	46	0.35	2.75 (0.56)	−0.67 (0.13)	−2.20 (0.67)	59	40–88	0.40	16	9–29
	Illinois	64	0.44	4.35 (0.64)	−0.93 (0.14)	−2.98 (0.60)	105	87–128	0.32	38	26–56
	Wisconsin	67	0.37	2.82 (0.45)	−0.76 (0.12)	−1.10 (0.76)	40	31–51	0.23	29	19–44
Combined	Minnesota	—	—	3.07 (0.15)	—	—	57	44–75	0.40	18	11–27
	Illinois	177	0.38	3.51 (0.35)	−0.76 (0.07)	−2.23 (0.37)	103	80–131	0.32	40	28–57
	Wisconsin	—	—	2.85 (0.14)	—	—	43	32–58	0.23	22	15–31

*Model fit to data from individual states separately, $r = b_0 + b_1D + b_2PBt$, or to the three states combined, but with differences among states reflected by state-specific intercepts. †Mean densities of larvae were estimated by setting $r = 0$ and solving for $N^* = \exp[-(b_0 + b_2PBt)/b_1]$ (see Fig. 3). Mean for pre-Bt era used $PBt = 0$; Bt era used 14-year average PBt. Confidence intervals (95% CIs) were estimated with the delta method (*18*) in log scale and then back-transformed to arithmetic scale.

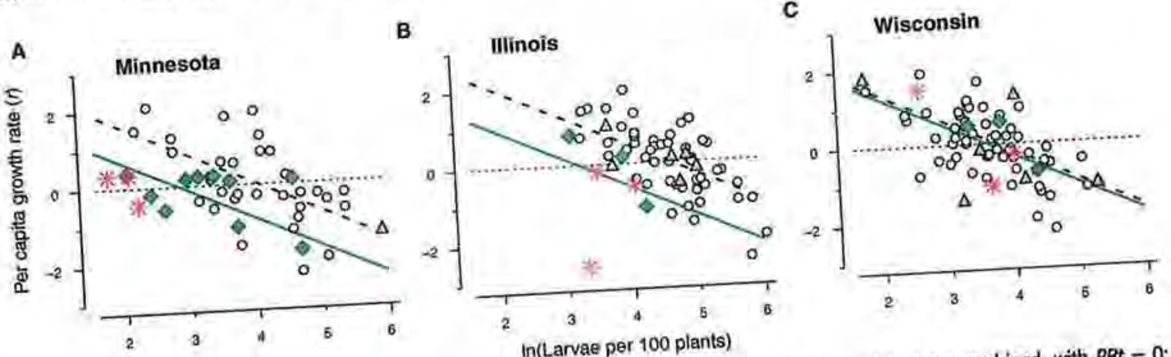

Fig. 3. Effects of Bt maize adoption on relation between larval density and annual per capita growth rates of *O. nubilalis* larval populations in non-Bt maize in three U.S. states: **(A)** Minnesota, **(B)** Illinois, **(C)** Wisconsin. Symbols indicate level of Bt maize adoption: open circles, pre-Bt years; gray triangles, 1 to 25%; green diamonds, 26 to 50%; orange asterisks, >51%. Bold dashed black line is least-squares fit for main-effects model, states combined, with $PBt = 0$; green line is same with PBt equal to respective statewide 14-year average (Table 1). Intersections between dotted lines at $r = 0$ and bold dashed lines indicate estimated mean density before adoption of Bt maize, and intersections with green solid lines show extent to which density declined with adoption of Bt maize in each state (Table 1).

the proportion of maize planted to Bt averaged 0.40 (i.e., 40% adoption), mean density declined by ~73% to ~16 larvae per 100 plants. In Illinois and Wisconsin, where respective average Bt adoption levels were 32% and 23%, mean densities were reduced by ~64% and ~27%, respectively. Similar reductions in estimated mean densities were observed when data from all three states were analyzed together (Table 1) and when landscape-level means from Bt fields and non-Bt fields were analyzed (*18*) (table S3 and fig. S2). Although many factors are known to affect *O. nubilalis* population dynamics, including weather and natural enemies (*3*, *12*, *16*, *19*), these results indicate that reductions in *O. nubilalis* were associated with commercialization of Bt maize.

Of the five states analyzed, Iowa, Illinois, Nebraska, and Minnesota are the top four maize-producing states in the United States, with yields in 2009 valued at $27.1 billion (*18*) (tables S1 and S4). Combining analysis of the larval and moth data with annual USDA data for maize yield, price, and planted area, we estimated the annual benefits from 1996 to 2009 for both Bt- and non-Bt maize growers in each state (*18*). Direct benefits for Bt maize growers were calculated as the value of the yield gain for Bt maize relative to non-Bt maize, minus the additional cost for Bt maize seed (*18*) (tables S4 and S5). Suppression benefits for non-Bt maize growers were calculated as the value of avoided yield losses under the assumption that the *O. nubilalis* populations in each state would have remained at their respective historical averages if Bt maize had not been commercialized. What actual *O. nubilalis* populations would have actually been without commercialization of Bt maize cannot be determined. However, midwestern farmers expected continual problems, as 67% of midwestern farmers reported in 1997 that *O. nubilalis* was a consistent problem in their fields (*10*). Mean yield losses for our analysis were calculated on the basis of *O. nubilalis* population densities and estimated models of larval stalk tunneling and associated yield loss (*23*, *24*). Calculations used observed statewide survey densities for Illinois, Minnesota, and Wisconsin. For Iowa and Nebraska, observed average larval densities collected at research plots at locations around the state were used when available (1997, 2000, 2001, and 2002); otherwise, larval densities were estimated from historical averages at a few locations and the observed proportional larval decline in Minnesota, a state with Bt maize adoption rates similar to Iowa and Nebraska (*18*) (Fig. 1, table S1, and supplemental documentation file). Given the different nature of these larval data, loss estimates for Iowa and Nebraska are reported separately.

On the basis of these calculations, we estimate that cumulative benefits for both Bt and non-Bt maize growers during the past 14 years were almost $6.9 billion in the five-state region (18.7 million ha in 2009)—more than $3.2 billion in Illinois, Minnesota, and Wisconsin, and $3.6 billion in Iowa and Nebraska (Fig. 4). Of this $6.9 billion total, cumulative suppression benefits to non-Bt maize growers resulting from *O. nubilalis* population suppression in non-Bt maize exceeded $4.3 billion—more than $2.4 billion in Illinois, Minnesota, and Wisconsin, and $1.9 billion in Iowa and Nebraska—or about 63% of the total benefits. Direct benefits for Bt maize growers (Fig. 4, A and B) were reduced because of the additional cost for Bt seed over the 14 growing seasons, which we estimate to have a cumulative value of almost $1.7 billion, whereas non-Bt maize experienced lower *O. nubilalis* damage as a result of areawide suppression at no additional cost.

In Illinois, Minnesota, and Wisconsin, suppression benefits for non-Bt maize growers (Fig. 4C) were initially larger (albeit dominated by Illinois and Minnesota) but more quickly exceeded the direct benefits for Bt maize, because population suppression occurred more rapidly than in Iowa and Nebraska (Fig. 4D). In Iowa and Nebraska, total grower benefits were larger because initial long-term population densities were greater. From 2007 onward, cumulative benefits for non-Bt maize growers exceeded benefits for Bt maize growers because suppression had become more effective.

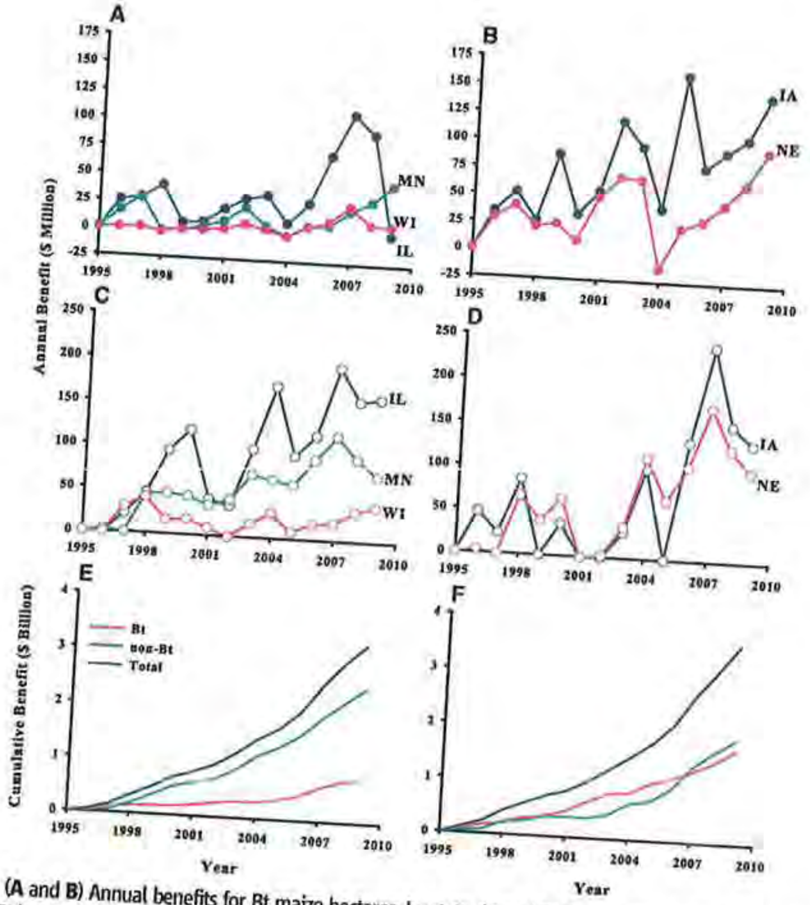

Fig. 4. (**A** and **B**) Annual benefits for Bt maize hectares, by state. (**C** and **D**) Annual pest suppression benefits for non-Bt hectares, by state. (**E** and **F**) Cumulative benefits across states. Benefits are expressed in 2009 dollars.

These benefit estimates do not incorporate effects of price changes and shifts in planted area that would have resulted without commercialization of Bt maize. Nevertheless, the calculations serve to indicate the potential magnitude of maize supply increase, and its market value resulting from areawide suppression of *O. nubilalis* in these five states.

Regional reductions in the pink bollworm (*Pectinophora gossypiella*), which is fairly specialized to cotton (near-monophagous), have been reported from the use of Bt cotton in the United States (*25*). Also, areawide suppression of the polyphagous lepidopteran pest *Helicoverpa armigera* by Bt cotton in China has been reported (*26*). Reductions in *O. nubilalis* populations related to Bt maize have also been reported in other parts of the United States (*27*). We show here that pest suppression is directly associated with the use of transgenic maize. In addition, our findings indicate that economic benefits accrue not only to farmers planting Bt maize, but also to those planting non-Bt maize as a result of areawide pest suppression, and that these suppression benefits can equal or exceed the benefits to Bt maize growers.

These results highlight the need to account for economic benefits of pest suppression for non-Bt maize, as well as for direct economic benefits of Bt maize (*28*). Moreover, as *O. nubilalis* is highly polyphagous, the observed regional population declines suggest that traditional and organic farmers growing other crops might also benefit (*29*). Sustained economic and environmental benefits of this technology, however, will depend on continued stewardship by producers to maintain non-Bt maize refugia (*5*, *7–10*) to minimize the risk of evolution of Bt resistance in crop pest species, and also on the dynamics of Bt resistance evolution at low pest densities and for variable pest phenotypes (*30*, *31*).

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Supporting Online Material

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Figs. S1 and S2
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A Meta-Analysis of the Impacts of Genetically Modified Crops

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Abstract

Background: Despite the rapid adoption of genetically modified (GM) crops by farmers in many countries, controversies about this technology continue. Uncertainty about GM crop impacts is one reason for widespread public suspicion.

Objective: We carry out a meta-analysis of the agronomic and economic impacts of GM crops to consolidate the evidence.

Data Sources: Original studies for inclusion were identified through keyword searches in ISI Web of Knowledge, Google Scholar, EconLit, and AgEcon Search.

Study Eligibility Criteria: Studies were included when they build on primary data from farm surveys or field trials anywhere in the world, and when they report impacts of GM soybean, maize, or cotton on crop yields, pesticide use, and/or farmer profits. In total, 147 original studies were included.

Synthesis Methods: Analysis of mean impacts and meta-regressions to examine factors that influence outcomes.

Results: On average, GM technology adoption has reduced chemical pesticide use by 37%, increased crop yields by 22%, and increased farmer profits by 68%. Yield gains and pesticide reductions are larger for insect-resistant crops than for herbicide-tolerant crops. Yield and profit gains are higher in developing countries than in developed countries.

Limitations: Several of the original studies did not report sample sizes and measures of variance.

Conclusion: The meta-analysis reveals robust evidence of GM crop benefits for farmers in developed and developing countries. Such evidence may help to gradually increase public trust in this technology.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

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Introduction

Despite the rapid adoption of genetically modified (GM) crops by farmers in many countries, public controversies about the risks and benefits continue [1–4]. Numerous independent science academies and regulatory bodies have reviewed the evidence about risks, concluding that commercialized GM crops are safe for human consumption and the environment [5–7]. There are also plenty of studies showing that GM crops cause benefits in terms of higher yields and cost savings in agricultural production [8–12], and welfare gains among adopting farm households [13–15]. However, some argue that the evidence about impacts is mixed and that studies showing large benefits may have problems with the data and methods used [16–18]. Uncertainty about GM crop impacts is one reason for the widespread public suspicion towards this technology. We have carried out a meta-analysis that may help to consolidate the evidence.

While earlier reviews of GM crop impacts exist [19–22], our approach adds to the knowledge in two important ways. First, we include more recent studies into the meta-analysis. In the emerging literature on GM crop impacts, new studies are published continuously, broadening the geographical area covered, the methods used, and the type of outcome variables considered. For instance, in addition to other impacts we analyze effects of GM crop adoption on pesticide quantity, which previous meta-analyses could not because of the limited number of observations for this particular outcome variable. Second, we go beyond average impacts and use meta-regressions to explain impact heterogeneity and test for possible biases.

Our meta-analysis concentrates on the most important GM crops, including herbicide-tolerant (HT) soybean, maize, and cotton, as well as insect-resistant (IR) maize and cotton. For these crops, a sufficiently large number of original impact studies have been published to estimate meaningful average effect sizes. We estimate mean impacts of GM crop adoption on crop yield, pesticide quantity, pesticide cost, total production cost, and farmer profit. Furthermore, we analyze several factors that may influence outcomes, such as geographic location, modified crop trait, and type of data and methods used in the original studies.

Materials and Methods

Literature search

Original studies for inclusion in this meta-analysis were identified through keyword searches in relevant literature databanks. Studies were searched in the ISI Web of Knowledge, Google Scholar, EconLit, and AgEcon Search. We searched for studies in the English language that were published after 1995. We did not extend the review to earlier years, because the commercial adoption of GM crops started only in the mid-1990s [23]. The search was performed for combinations of keywords related to GM technology and related to the outcome of interest. Concrete keywords used related to GM technology were (an asterisk is a replacement for any ending of the respective term; quotation marks indicate that the term was used as a whole, not each word alone): GM*, "genetically engineered", "genetically modified", transgenic, "agricultural biotechnology", HT, "herbicide tolerant", Roundup, Bt, "insect resistant". Concrete keywords used related to outcome variables were: impact*, effect*, benefit*, yield*, economic*, income*, cost*, soci*, pesticide*, herbicide*, insecticide*, productivity*, margin*, profit*. The search was completed in March 2014.

Most of the publications in the ISI Web of Knowledge are articles in academic journals, while Google Scholar, EconLit, and AgEcon Search also comprise book chapters and grey literature such as conference papers, working papers, and reports in institutional series. Articles published in academic journals have usually passed a rigorous peer-review process. Most papers presented at academic conferences have also passed a peer-review process, which is often less strict than that of good journals though. Some of the other publications are peer reviewed, while many are not. Some of the working papers and reports are published by research institutes or government organizations, while others are NGO publications. Unlike previous reviews of GM crop impacts, we did not limit the sample to peer-reviewed studies but included all publications for two reasons. First, a clear-cut distinction between studies with and without peer review is not always possible, especially when dealing with papers that were not published in a journal or presented at an academic conference [24]. Second, studies without peer review also influence the public and policy debate on GM crops; ignoring them completely would be short-sighted.

Of the studies identified through the keyword searches, not all reported original impact results. We classified studies by screening titles, abstracts, and full texts. Studies had to fulfill the following criteria to be included:

- The study is an empirical investigation of the agronomic and/or economic impacts of GM soybean, GM maize, or GM cotton using micro-level data from individual plots and/or farms. Other GM crops such as GM rapeseed, GM sugarbeet, and GM papaya were commercialized in selected countries [23], but the number of impact studies available for these other crops is very small.
- The study reports GM crop impacts in terms of one or more of the following outcome variables: yield, pesticide quantity (especially insecticides and herbicides), pesticide costs, total variable costs, gross margins, farmer profits. If only the number of pesticide sprays was reported, this was used as a proxy for pesticide quantity.
- The study analyzes the performance of GM crops by either reporting mean outcomes for GM and non-GM, absolute or percentage differences, or estimated coefficients of regression models that can be used to calculate percentage differences between GM and non-GM crops.
- The study contains original results and is not only a review of previous studies.

In some cases, the same results were reported in different publications; in these cases, only one of the publications was included to avoid double counting. On the other hand, several publications involve more than one impact observation, even for a single outcome variable, for instance when reporting results for different geographical regions or derived with different methods (e.g., comparison of mean outcomes of GM and non-GM crops plus regression model estimates). In those cases, all observations were included. Moreover, the same primary dataset was sometimes used for different publications without reporting identical results (e.g., analysis of different outcome variables, different waves of panel data, use of different methods). Hence, the number of impact observations in our sample is larger than the number of publications and primary datasets (Data S1). The number of studies selected at various stages is shown in the flow diagram in Figure 1. The number of publications finally included in the meta-analysis is 147 (Table S1).

Effect sizes and influencing factors

Effect sizes are measures of outcome variables. We chose the percentage difference between GM and non-GM crops for five different outcome variables, namely yield, pesticide quantity, pesticide cost, total production cost, and farmer profits per unit area. Most studies that analyze production costs focus on variable costs, which are the costs primarily affected through GM technology adoption. Accordingly, profits are calculated as revenues minus variable production costs (profits calculated in this way are also referred to as gross margins). These production costs also take into account the higher prices charged by private companies for GM seeds. Hence, the percentage differences in profits considered here are net economic benefits for farmers using GM technology. Percentage differences, when not reported in the original studies, were calculated from mean value comparisons between GM and non-GM or from estimated regression coefficients.

Since we look at different types of GM technologies (different modified traits) that are used in different countries and regions, we do not expect that effect sizes are homogenous across studies. Hence, our approach of combining effect sizes corresponds to a random-effects model in meta-analysis [25]. To explain impact heterogeneity and test for possible biases, we also compiled data on a number of study descriptors that may influence the reported effect sizes. These influencing factors include information on the type of GM technology (modified trait), the region studied, the type of data and method used, the source of funding, and the type of publication. All influencing factors are defined as dummy variables. The exact definition of these dummy variables is given in Table 1. Variable distributions of the study descriptors are shown in Table S2.

Statistical analysis

In a first step, we estimate average effect sizes for each outcome variable. To test whether these mean impacts are significantly

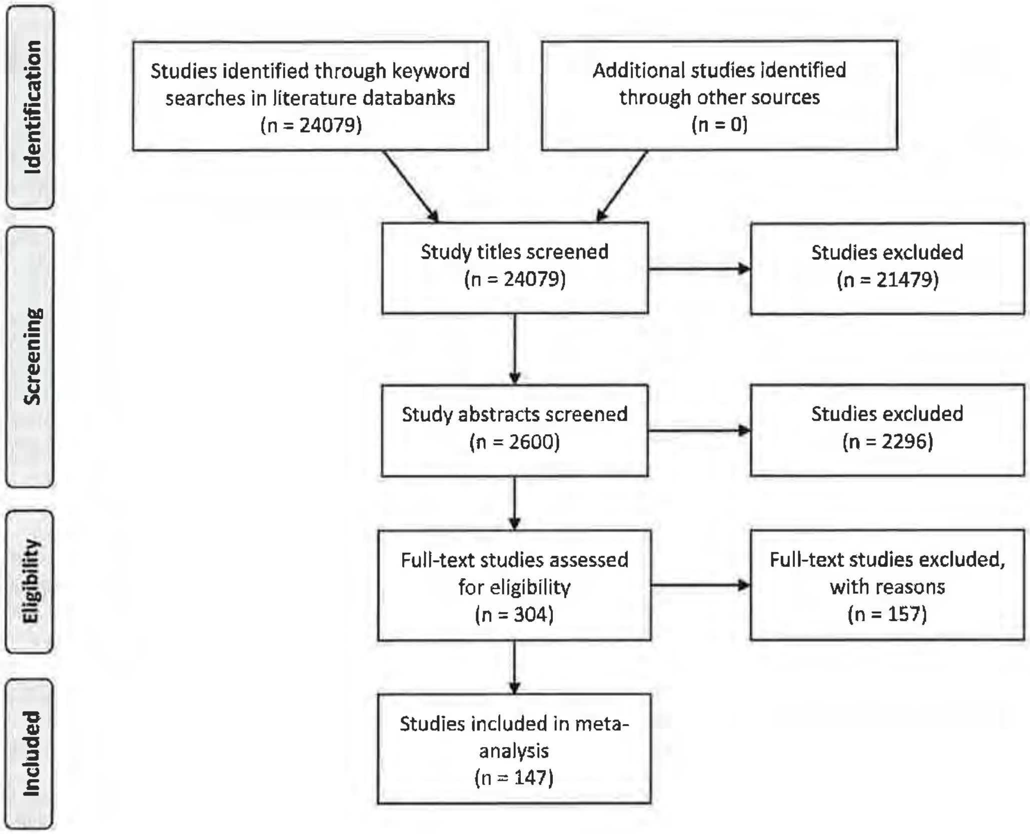

Figure 1. Selection of studies for inclusion in the meta-analysis.
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different from zero, we regress each outcome variable on a constant with cluster correction of standard errors by primary dataset. Thus, the test for significance is valid also when observations from the same dataset are correlated. We estimate average effect sizes for all GM crops combined. However, we expect that the results may differ by modified trait, so that we also analyze mean effects for HT crops and IR crops separately.

Meta-analyses often weight impact estimates by their variances; estimates with low variance are considered more reliable and receive a higher weight [26]. In our case, several of the original studies do not report measures of variance, so that weighting by variance is not possible. Alternatively, weighting by sample size is common, but sample sizes are also not reported in all studies considered, especially not in some of the grey literature publications. To test the robustness of the results, we employ a

Table 1. Variables used to analyze influencing factors of GM crop impacts.

Variable name	Variable definition
Insect resistance (IR)	Dummy that takes a value of one for all observations referring to insect-resistant GM crops with genes from *Bacillus thuringiensis* (Bt), and zero for all herbicide-tolerant (HT) GM crops.
Developing country	Dummy that takes a value of one for all GM crop applications in a developing country according to the World Bank classification of countries, and zero for all applications in a developed country.
Field-trial data	Dummy that takes a value of one for all observations building on field-trial data (on-station and on-farm experiments), and zero for all observations building on farm survey data.
Industry-funded study	Dummy that takes a value of one for all studies that mention industry (private sector companies) as source of funding, and zero otherwise.
Regression model result	Dummy that takes a value of one for all impact observations that are derived from regression model estimates, and zero for observations derived from mean value comparisons between GM and non-GM.
Journal publication	Dummy that takes a value of one for all studies published in a peer-reviewed journal, and zero otherwise.
Journal/academic conference	Dummy that takes a value of one for all studies published in a peer-reviewed journal or presented at an academic conference, and zero otherwise.

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different weighting procedure, using the inverse of the number of impact observations per dataset as weights. This procedure avoids that individual datasets that were used in several publications dominate the calculation of average effect sizes.

In a second step, we use meta-regressions to explain impact heterogeneity and test for possible biases. Linear regression models are estimated separately for all of the five outcome variables:

$$\%\Delta Y_{hij} = \alpha_h + \mathbf{X}_{hij}\boldsymbol{\beta}_h + \varepsilon_{hij}$$

$\%\Delta Y_{hij}$ is the effect size (percentage difference between GM and non-GM) of each outcome variable h for observation i in publication j, and $\mathbf{X}_{hij}$ is a vector of influencing factors. α_h is a coefficient and $\boldsymbol{\beta}_h$ a vector of coefficients to be estimated; ε_{hij} is a random error term. Influencing factors used in the regressions are defined in Table 1.

Results and Discussion

Average effect sizes

Distributions of all five outcome variables are shown in Figure S1. Table 2 presents unweighted mean impacts. As a robustness check, we weighted by the inverse of the number of impact observations per dataset. Comparing unweighted results (Table 2) with weighted results (Table S3) we find only very small differences. This comparison suggests that the unweighted results are robust.

On average, GM technology has increased crop yields by 21% (Figure 2). These yield increases are not due to higher genetic yield potential, but to more effective pest control and thus lower crop damage [27]. At the same time, GM crops have reduced pesticide quantity by 37% and pesticide cost by 39%. The effect on the cost of production is not significant. GM seeds are more expensive than non-GM seeds, but the additional seed costs are compensated through savings in chemical and mechanical pest control. Average profit gains for GM-adopting farmers are 69%.

Results of Cochran's test [25], which are reported in Figure S1, confirm that there is significant heterogeneity across study observations for all five outcome variables. Hence it is useful to further disaggregate the results. Table 2 shows a breakdown by modified crop trait. While significant reductions in pesticide costs are observed for both HT and IR crops, only IR crops cause a consistent reduction in pesticide quantity. Such disparities are expected, because the two technologies are quite different. IR crops protect themselves against certain insect pests, so that spraying can be reduced. HT crops, on the other hand, are not protected against pests but against a broad-spectrum chemical herbicide (mostly glyphosate), use of which facilitates weed control. While HT crops have reduced herbicide quantity in some situations, they have contributed to increases in the use of broad-spectrum herbicides elsewhere [2,11,19]. The savings in pesticide costs for HT crops in spite of higher quantities can be explained by the fact that broad-spectrum herbicides are often much cheaper than the selective herbicides that were used before. The average farmer profit effect for HT crops is large and positive, but not statistically significant because of considerable variation and a relatively small number of observations for this outcome variable.

Impact heterogeneity and possible biases

Table 3 shows the estimation results from the meta-regressions that explain how different factors influence impact heterogeneity. Controlling for other factors, yield gains of IR crops are almost 7 percentage points higher than those of HT crops (column 1). Furthermore, yield gains of GM crops are 14 percentage points higher in developing countries than in developed countries. Especially smallholder farmers in the tropics and subtropics suffer from considerable pest damage that can be reduced through GM crop adoption [27].

Most original studies in this meta-analysis build on farm surveys, although some are based on field-trial data. Field-trial results are often criticized to overestimate impacts, because farmers may not be able to replicate experimental conditions. However, results in Table 3 (column 1) show that field-trial data do not overestimate the yield effects of GM crops. Reported yield gains from field trials are even lower than those from farm surveys. This is plausible, because pest damage in non-GM crops is often more severe in farmers' fields than on well-managed experimental plots.

Table 2. Impacts of GM crop adoption by modified trait.

Outcome variable	All GM crops	Insect resistance	Herbicide tolerance
Yield	21.57*** (15.65; 27.48)	24.85*** (18.49; 31.22)	9.29** (1.78; 16.80)
n/m	451/100	353/83	94/25
Pesticide quantity	−36.93*** (−48.01; −25.86)	−41.67*** (−51.99; −31.36)	2.43 (−20.26; 25.12)
n/m	121/37	108/31	13/7
Pesticide cost	−39.15*** (−46.96; −31.33)	−43.43*** (−51.64; −35.22)	−25.29*** (−33.84; −16.74)
n/m	193/57	145/45	48/15
Total production cost	3.25 (−1.76; 8.25)	5.24** (0.25; 10.73)	−6.83 (−16.43; 2.77)
n/m	115/46	96/38	19/10
Farmer profit	68.21*** (46.31; 90.12)	68.78*** (46.45; 91.11)	64.29 (−24.73; 153.31)
n/m	136/42	119/36	17/9

Average percentage differences between GM and non-GM crops are shown with 95% confidence intervals in parentheses. *, **, *** indicate statistical significance at the 10%, 5%, and 1% level, respectively. *n* is the number of observations, *m* the number of different primary datasets from which these observations are derived.

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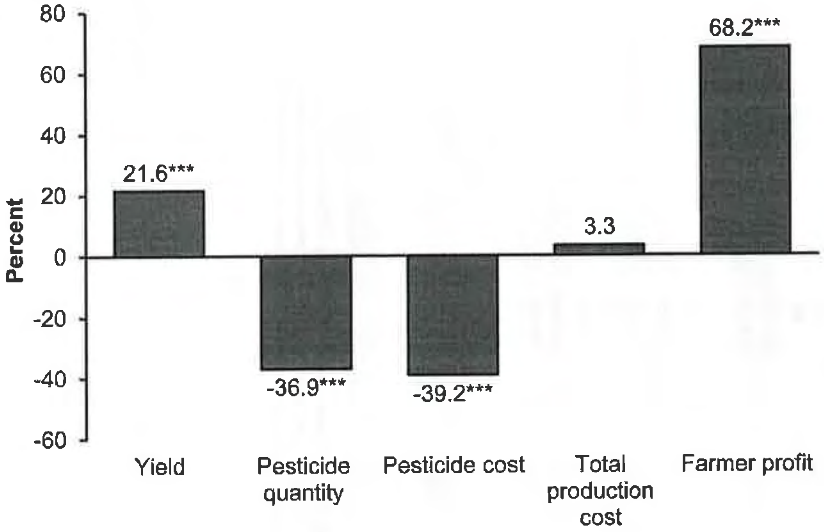

Figure 2. Impacts of GM crop adoption. Average percentage differences between GM and non-GM crops are shown. Results refer to all GM crops, including herbicide-tolerant and insect-resistant traits. The number of observations varies by outcome variable; yield: 451; pesticide quantity: 121; pesticide cost: 193; total production cost: 115; farmer profit: 136. *** indicates statistical significance at the 1% level.
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Another concern often voiced in the public debate is that studies funded by industry money might report inflated benefits. Our results show that the source of funding does not significantly influence the impact estimates. We also analyzed whether the statistical method plays a role. Many of the earlier studies just compared yields of GM and non-GM crops without considering possible differences in other inputs and conditions that may also affect the outcome. Net impacts of GM technology can be estimated with regression-based production function models that control for other factors. Interestingly, results derived from regression analysis report higher average yield effects.

Finally, we examined whether the type of publication matters. Controlling for other factors, the regression coefficient for journal publications in column (1) of Table 3 implies that studies published in peer-reviewed journals show 12 percentage points higher yield gains than studies published elsewhere. Indeed, when only including observations from studies that were published in journals, the mean effect size is larger than if all observations are included (Figure S2). On first sight, one might suspect publication bias, meaning that only studies that report substantial effects are accepted for publication in a journal. A common way to assess possible publication bias in meta-analysis is through funnel plots [25], which we show in Figure S3. However, in our case these funnel plots should not be over-interpreted. First, only studies that report variance measures can be included in the funnel plots, which holds true only for a subset of the original studies used here. Second, even if there were publication bias, our mean results would be estimated correctly, because we do include studies that were not published in peer-reviewed journals.

Further analysis suggests that the journal review process does not systematically filter out studies with small effect sizes. The journal articles in the sample report a wide range of yield effects, even including negative estimates in some cases. Moreover, when combining journal articles with papers presented at academic conferences, average yield gains are even higher (Table 3, column 2). Studies that were neither published in a journal nor presented at an academic conference encompass a diverse set of papers, including reports by NGOs and outspoken biotechnology critics. These reports show lower GM yield effects on average, but not all meet common scientific standards. Hence, rather than indicating publication bias, the positive and significant journal coefficient may be the result of a negative NGO bias in some of the grey literature.

Concerning other outcome variables, IR crops have much stronger reducing effects on pesticide quantity than HT crops (Table 3, column 3), as already discussed above. In terms of pesticide costs, the difference between IR and HT is less pronounced and not statistically significant (column 4). The profit gains of GM crops are 60 percentage points higher in developing countries than in developed countries (column 6). This large difference is due to higher GM yield gains and stronger pesticide cost savings in developing countries. Moreover, most GM crops are not patented in developing countries, so that GM seed prices are lower [19]. Like for yields, studies published in peer-reviewed journals report higher profit gains than studies published elsewhere, but again we do not find evidence of publication bias (column 7).

Conclusion

This meta-analysis confirms that – in spite of impact heterogeneity – the average agronomic and economic benefits of GM crops are large and significant. Impacts vary especially by modified crop trait and geographic region. Yield gains and pesticide reductions are larger for IR crops than for HT crops. Yield and farmer profit gains are higher in developing countries than in developed countries. Recent impact studies used better data and methods than earlier studies, but these improvements in study design did not reduce the estimates of GM crop advantages. Rather, NGO reports and other publications without scientific peer review seem to bias the impact estimates downward. But even with such biased estimates included, mean effects remain sizeable.

One limitation is that not all of the original studies included in this meta-analysis reported sample sizes and measures of variance. This is not untypical for analyses in the social sciences, especially when studies from the grey literature are also included. Future

Table 3. Factors influencing results on GM crop impacts (%).

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Variables	**Yield**	**Yield**	**Pesticide quantity**	**Pesticide cost**	**Total cost**	**Farmer profit**	**Farmer profit**
Insect resistance (IR)	6.58** (2.85)	5.25* (2.82)	-37.38*** (11.81)	-7.23 (5.44)	5.63 (5.60)	-22.33 (21.62)	-33.41 (21.94)
Developing country	14.17*** (2.72)	13.32*** (2.65)	-10.23 (8.99)	-19.16*** (5.35)	3.43 (4.78)	59.52*** (18.02)	60.58*** (17.67)
Field-trial data	-7.14** (3.19)	-7.81** (3.08)	–#	-17.56 (11.45)	-10.69* (5.79)	–#	–#
Industry-funded study	1.68 (5.30)	1.05 (5.21)	37.04 (23.08)	-7.77 (10.22)	–#	–#	–#
Regression model result	7.38* (3.90)	7.29* (3.83)	9.67 (10.40)	–#	–#	-11.44 (24.33)	-9.85 (24.03)
Journal publication	12.00*** (2.52)	–	9.95 (6.79)	-3.71 (4.09)	-3.08 (3.30)	48.27*** (15.48)	–
Journal/academic conference	–	16.48*** (2.64)	–	–	–	–	65.29*** (17.75)
Constant	-0.22 (2.84)	-2.64 (2.86)	-4.44 (10.33)	-16.13 (4.88)	-1.02 (4.86)	8.57 (24.33)	-1.19 (24.53)
Observations	451	451	121	193	115	136	136
R^2	0.23	0.25	0.20	0.14	0.12	0.12	0.14

Coefficient estimates from linear regression models are shown with standard errors in parentheses. Dependent variables are GM crop impacts measured as percentage differences between GM and non-GM. All explanatory variables are 0/1 dummies (for variable definitions see Table 1). The yield models in columns (1) and (2) and the farmer profit models in columns (6) and (7) have the same dependent variables, but they differ in terms of the explanatory variables, as shown. *, **, *** indicate statistical significance at the 10%, 5%, and 1% level, respectively. # indicates that the variable was dropped because the number of observations with a value of one was smaller than 5.

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impact studies with primary data should follow more standardized reporting procedures. Nevertheless, our findings reveal that there is robust evidence of GM crop benefits. Such evidence may help to gradually increase public trust in this promising technology.

Supporting Information

Figure S1 Histograms of effect sizes for the five outcome variables.
(PDF)

Figure S2 Impacts of GM crop adoption including only studies published in journals.
(PDF)

Figure S3 Funnel plots for the five outcome variables.
(PDF)

Table S1 List of publications included in the meta-analysis.
(PDF)

Table S2 Distribution of study descriptor dummy variables for different outcomes.
(PDF)

Table S3 Weighted mean impacts of GM crop adoption.
(PDF)

Data S1 Data used for the meta-analysis.
(PDF)

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Author Contributions

Conceived and designed the research: WK MQ. Analyzed the data: WK MQ. Contributed to the writing of the manuscript: WK MQ. Compiled the data: WK.

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Key global economic and environmental impacts
of genetically modified (GM) rop use 1996-2012

KEYWORDS: yield, cost, income, production, genetically modified crops, pesticide, carbon sequestration, no tillage, environmental impact quotient

Abstract

This paper summarises the economic and key environmental impacts that crop biotechnology has had on global agriculture. The analysis shows that there have been very significant net economic benefits at the farm level amounting to \$18.8 billion in 2012 and \$116.6 billion for the seventeen year period 1996-2012 (in nominal terms). These economic gains have been divided roughly 50 percent each to farmers in developed and developing countries. GM technology have also made important contributions to increasing global production levels of the four main crops, having added 122 million tonnes and 230 million tonnes respectively, to the global production of soybeans and maize since the introduction of the technology in the mid-1990s. In terms of key environmental impacts, the adoption of the technology has reduced pesticide spraying by 503 million kg (-8.8 percent) and, as a result, decreased the environmental impact associated with herbicide and insecticide use on these crops (as measured by the indicator the Environmental Impact Quotient (EIQ)) by18.7 percent. The technology has also facilitated a significant reduction in the release of greenhouse gas emissions from this cropping area, which, in 2012, was equivalent to removing 11.88 million cars from the roads.

INTRODUCTION

This paper provides insights into the reasons why so many farmers around the world have adopted crop biotechnology and continue to use it in their production systems since the technology first became available on a widespread commercial basis in the mid-1990s. The paper draws, and is largely based on, the considerable body of peer reviewed literature available that has examined these issues. It specifically focuses on the farm level economic effects, the production effects, the environmental impact resulting from changes in the use of insecticides and herbicides, and the contribution towards reducing greenhouse gas (GHG) emissions.

The report is based on extensive analysis of existing farm level impact data for biotech crops. Whilst primary data for impacts of commercial cultivation were not available for every crop, in every year and for each country, a substantial body of representative research and analysis is available and this has been used as the basis for the analysis presented. This has been supplemented by the authors' own data collection and analysis. The analysis of pesticide usage also takes into consideration changes in the pattern of herbicide use in recent years that reflect measures taken by some farmers to address issues of weed resistance to the main herbicide (glyphosate) used with herbicide tolerant biotech crops. For additional information on the methodology, data sources and references (1), readers should consult a detailed examination of these issues in *Brookes G and Barfoot P (2014) GM crops: global socio-economic and environmental impacts 1996-2012, available at www.pgeconomics.co.uk.*

ECONOMIC IMPACTS

GM technology has had a significant positive impact on farm income derived from a combination of enhanced productivity and efficiency gains (Table 1). In 2012, the direct global farm income benefit from GM crops was \$18.8 billion. This is equivalent to having added 5.6 percent to the value of global production of the four main crops of soybeans, maize, canola and cotton. Since 1996, farm incomes have increased by \$116.6 billion.

The largest gains in farm income in 2012 have arisen in the maize sector, largely from yield gains. The \$6.7 billion additional income generated by GM insect resistant (GM IR) maize in 2012 has been equivalent to adding 6.6 percent to the value of the crop in the GM crop growing countries, or adding the equivalent of 3 percent to the \$226 billion value of the global maize crop in 2012. Cumulatively since 1996, GM IR technology has added \$32.3 billion to the income of global maize farmers.

Substantial gains have also arisen in the cotton sector through a combination of higher yields and lower costs. In 2012, cotton farm income levels in the GM adopting countries increased by $5.5 billion and since 1996, the sector has benefited from an additional $37.7 billion. The 2012 income gains are equivalent to adding 13.5 percent to the value of the cotton crop in these countries, or 11.5 percent to the $47 billion value of total global cotton production. This is a substantial increase in value added terms for two new cotton seed technologies.

Significant increases to farm incomes have also resulted in the soybean and canola sectors. The GM HT technology in soybeans has boosted farm incomes by $4.8 billion in 2012, and since 1996 has delivered over $37 billion of extra farm income. In the canola sector (largely North American) an additional $3.66 billion has been generated (1996-2012).

Table 2 summarises farm income impacts in key GM crop adopting countries. This highlights the important farm income benefit arising from GM HT soybeans in South America (Argentina, Bolivia, Brazil, Paraguay and Uruguay), GM IR cotton in China and India and a range of GM cultivars in the US. It also illustrates the growing level of farm income benefits being obtained in South Africa, the Philippines, Mexico and Colombia.

In terms of the division of the economic benefits obtained by farmers in developing countries relative to farmers in developed countries, Table 3 shows that in 2012, 46.2 percent of the farm income benefits have been earned by developing country farmers. The vast majority of these income gains for developing country farmers have been from GM IR cotton and GM HT soybeans. Over the seventeen years, 1996-2012, the cumulative farm income gain derived by developing country farmers was 49.9 percent ($58.15 billion).

Examining the cost farmers pay for accessing GM technology, Table 4 shows that across the four main GM crops, the total cost in 2012 was equal to 23 percent of the total technology gains (inclusive of farm income gains plus cost of the technology payable to the seed supply chain (2)).

For farmers in developing countries the total cost was equal to 21 percent of total technology gains, whilst for farmers in developed countries the cost was 25 percent of the total technology gains. Whilst circumstances vary between countries, the higher share of total technology gains accounted for by farm income gains in developing countries, relative to the farm income share in developed countries, reflects factors such as weaker provision and enforcement of intellectual property rights in developing countries and the higher average level of farm income gain on a per hectare basis derived by developing country farmers relative to developed country farmers.

Notes: All values are nominal. Others = Virus resistant papaya and squash and herbicide tolerant sugar beet. Totals for the value shares exclude 'other crops' (ie, relate to the 4 main crops of soybeans, maize, canola and cotton). Farm income calculations are net farm income changes after inclusion of impacts on yield, crop quality and key variable costs of production (eg, payment of seed premia, impact on crop protection expenditure)

Trait	Increase in farm income 2012	Increase in farm income 1996-2012	Farm income benefit in 2012 as percent of total value of production of these crops in GM adopting countries	Farm income benefit in 2012 as percent of total value of global production of crop
GM herbicide tolerant soybeans	4,797.9	37,008.9	4.4	4.0
GM herbicide tolerant maize	1,197.9	5,413.7	1.2	0.5
GM herbicide tolerant cotton	147.2	1,371.6	0.4	0.3
GM herbicide tolerant canola	481.0	3,664.4	4.9	1.3
GM insect resistant maize	6,727.8	32,317.2	6.5	3.5
GM insect resistant cotton	5,331.3	36,317.2	13.1	11.2
Others	82.3	426.7	Not applicable	Not applicable
Totals	18,765.4	116,590.4	6.8	5.8

Notes: All values are nominal. Others = Virus resistant papaya and squash and herbicide tolerant sugar beet. Totals for the value shares exclude 'other crops' (ie, relate to the 4 main crops of soybeans, maize, canola and cotton). Farm income calculations are net farm income changes after inclusion of impacts on yield, crop quality and key variable costs of production (eg, payment of seed premia, impact on crop protection expenditure)

Table 1 Global farm income benefits from growing GM crops 1996-2012: million US $

	GM HT soybeans	GM HT maize	GM HT cotton	GM HT canola	GM IR maize	GM IR cotton	Total
US	18,668.7	3,262.5	975.8	268.5	26,375.6	4,045.7	53,087.7
Argentina	13,738.5	160.7	107.0	N/a	495.2	455.4	15,583.8
Brazil	4,825.6	103.4	92.5	N/a	3,361.7	13.3	8,396.5
Paraguay	828	N/a	N/a	N/a	N/a	N/a	828.0
Canada	356	81.3	N/a	3,366.8	1,042.9	N/a	4,851.0
South Africa	9.1	4.1	3.2	N/a	1,100.6	34.2	1,151.2
China	N/a	N/a	N/a	N/a	N/a	15,270.4	15,270.4
India	N/a	N/a	N/a	N/a	N/a	14,557.1	14,557.1
Australia	N/a	N/a	78.6	27.3	N/a	659.6	765.5
Mexico	5.0	N/a	90.4	N/a	N/a	136.6	232.0
Philippines	N/a	104.7	N/a	N/a	273.6	N/a	378.3
Romania	44.6	N/a	N/a	N/a	N/a	N/a	44.6
Uruguay	103.8	N/a	N/a	N/a	17.6	N/a	121.4
Spain	N/a	N/a	N/a	N/a	176.3	N/a	176.3
Other EU	N/a	N/a	N/a	N/a	18.8	N/a	18.8
Colombia	N/a	1.7	18.1	N/a	47.4	15.4	82.6
Bolivia	437.2	N/a	N/a	N/a	N/a	N/a	437.2
Burma	N/a	N/a	N/a	N/a	N/a	215.4	215.4
Pakistan	N/a	N/a	N/a	N/a	N/a	725.1	725.1
Burkina Faso	N/a	N/a	N/a	N/a	N/a	186.0	186.0
Honduras	N/a	N/a	N/a	N/a	8.9	N/a	8.9

Notes: All values are nominal. Farm income calculations are net farm income changes after inclusion of impacts on yield, crop quality and key variable costs of production (eg, payment of seed premia, impact on crop protection expenditure). *N/a* = not applicable. US total figure also includes $491 million for other crops/traits (not included in the table). Also not included in the table is $5.5 million extra farm income from GM HT sugar beet in Canada

Table 2 GM crop farm income benefits 1996-2012 selected countries: million US $

	Developed	Developing
GM HT soybeans	2,955.4	1,842.5
GM HT maize	654.0	543.9
GM HT cotton	71.4	75.8
GM HT canola	481.0	0
GM IR maize	5,327.5	1,400.3
GM IR cotton	530.7	4,800.7
GM virus resistant papaya and squash and GM HT sugar beet	86.5	0
Total	10,106.2	8,663.2

Developing countries = all countries in South America, Mexico, Honduras, Burkina Faso, India, China, the Philippines and South Africa

Table 3 GM crop farm income benefits 2012: developing versus developed countries: million US $

	Cost of technology: all farmers	Farm income gain: all farmers	Total benefit of technology to farmers and seed supply chain	Cost of technology, developing countries	Farm income gain: developing countries	Total benefit of technology to farmers and seed supply chain developing countries
GM HT soybeans	1,574.1	4,797.9	6,372.0	998.7	1,842.5	2,841.2
GM HT maize	1,059.4	1,197.9	2,257.3	384.5	543.9	928.4
GM HT cotton	295.0	147.2	442.2	22.2	75.8	98.0
GM HT canola	161.2	481.0	642.2	N/a	N/a	N/a
GM IR maize	1,800.8	6,727.8	8,528.6	512.3	1,400.3	1,912.6
GM IR cotton	720.7	5,331.3	6,052.0	422.7	4,800.7	5,223.4
Others	79.2	82.3	162.5	N/a	N/a	N/a
Total	5,641.4	18,765.4	24,410.8	2,340.4	8,663.2	10,983.6

N/a = not applicable. Cost of accessing technology based on the seed premia paid by farmers for using GM technology relative to its conventional equivalents

Table 4 Cost of accessing GM technology (million $) relative to the total farm income benefits 2012

PRODUCTION EFFECTS OF THE TECHNOLOGY

Based on the yield impacts used in the direct farm income benefit calculations above and taking account of the second soybean crop facilitation in South America, GM crops have added important volumes to global production of maize, cotton, canola and soybeans since 1996 (Table 5).

	1996-2012 additional production (million tonnes)	2012 additional production (million tonnes)
Soybeans	122.3	12.0
Maize	231.4	34.1
Cotton	19.2	2.4
Canola	6.5	0.8
Sugar beet	0.6	0.16

Note: GM HT sugar beet only in the US and Canada since 2008

Table 5. Additional crop production arising from positive yield effects of GM crops

The GM IR traits, used in maize and cotton, have accounted for 97.1 percent of the additional maize production and 99.3 percent of the additional cotton production. Positive yield impacts from the use of this technology have occurred in all user countries (except for GM IR cotton in Australia (3)) when compared to average yields derived from crops using conventional technology (such as application of insecticides and seed treatments). The average yield impact across the total area planted to these traits over the 17 years since 1996 has been +10.4 percent for maize and +16.1 percent for cotton.

The primary impact of GM HT technology has been to provide more cost effective (less expensive) and easier weed control, as opposed to improving yields. The improved weed control has, nevertheless, delivered higher yields in some countries. The main source of additional production from this technology has been via the facilitation of no tillage production system, shortening the production cycle and how it has enabled many farmers in South America to plant a crop of soybeans immediately after a wheat crop in the same growing season. This second crop, additional to traditional soybean production, has added 114.3 million tonnes to soybean production in Argentina and Paraguay between 1996 and 2012 (accounting for 93.5 percent of the total GM-related additional soybean production).

ENVIRONMENTAL IMPACT FROM CHANGES IN INSECTICIDE AND HERBICIDE USE

To examine this impact, the study has analysed both active ingredient use and utilised the indicator known as the Environmental Impact Quotient (EIQ) to assess the broader impact on the environment (plus impact on animal and human health). The EIQ distils the various environmental and health impacts of individual pesticides in different GM and conventional production systems into a single 'field value per hectare' and draws on key toxicity and environmental exposure data related to individual products. It therefore provides a better measure to contrast and compare the impact of various pesticides on the environment and human health than weight of active ingredient alone. Readers should, however, note that the EIQ is an indicator only (primarily of toxicity) and does not take into account all environmental issues and impacts. In the analysis of GM HT technology we have assumed that the conventional alternative delivers the same level of weed control as occurs in the GM HT production system.

GM traits have contributed to a significant reduction in the environmental impact associated with insecticide and herbicide use on the areas devoted to GM crops (Table 6). Since 1996, the use of pesticides on the GM crop area was reduced by 503 million kg of active ingredient (8.8 percent reduction), and the environmental impact associated with herbicide and insecticide use on these crops, as measured by the EIQ indicator, fell by18.7 percent.

Trait	Change in volume of active ingredient used (million kg)	Change in field EIQ impact (in terms of million field EIQ/ha units)	percent change in ai use on GM crops	percent change in environmental impact associated with herbicide & insecticide use on GM crops	Area GM trait 2012 (million ha)
GM herbicide tolerant soybeans	-4.7	-6,654	-0.2	-15.0	79.1
GM herbicide tolerant maize	-203.2	-6,925	-9.8	-13.3	38.5
GM herbicide tolerant canola	-15.0	-509	-16.7	-26.6	8.0
GM herbicide tolerant cotton	-16.3	-460	-6.8	-9.0	4.6
GM insect resistant maize	-57.6	-2,215	-47.9	-45.3	42.7
GM insect resistant cotton	-205.4	-9,256	-25.6	-28.2	22.1
GM herbicide tolerant sugar beet	+1.3	-2	+29.2	-2.0	0.51
Totals	-503.1	-25,121	-8.8	-18.7	

Table 6. Impact of changes in the use of herbicides and insecticides from growing GM crops globally 1996-2012

In absolute terms, the largest environmental gain has been associated with the adoption of GM insect resistant (IR) technology. GM IR cotton has contributed a 25.6 percent reduction in the volume of active ingredient used and a 28.2 percent reduction in the EIQ indicator (1996-2012) due to the significant reduction in insecticide use that the technology has facilitated, in what has traditionally been an intensive user of insecticides. Similarly, the use of GM IR technology in maize has led to important reductions in insecticide use, with associated environmental benefits.

The volume of herbicides used in GM maize crops also decreased by 203 million kg (1996-2012), a 9.8 percent reduction, whilst the overall environmental impact associated with herbicide use on these crops decreased by a significantly larger 13.3 percent. This highlights the switch in herbicides used with most GM herbicide tolerant (HT) crops to active ingredients with a more environmentally benign profile than the ones generally used on conventional crops.

Important environmental gains have also arisen in the soybean and canola sectors. In the soybean sector, herbicide use decreased by 4.7 million kg (1996-2012) and the associated environmental impact of herbicide use on this crop area decreased, due to a switch to more environmentally benign herbicides (-15 percent). In the canola sector, farmers reduced herbicide use by 15 million kg (a 16.7 percent reduction) and the associated environmental impact of herbicide use on this crop area fell by 26.6 percent (due to a switch to more environmentally benign herbicides).

In terms of the division of the environmental benefits associated with less insecticide and herbicide use for farmers in developed countries relative to farmers in developing countries, Table 7 shows a 54 percent:46 percent split of the environmental benefits (1996-2012) respectively in developed (54 percent) and developing countries (46 percent). About three-quarters (73 percent) of the environmental gains in developing countries have been from the use of GM IR cotton.

It should, however, be noted that in some regions where GM HT crops have been widely grown, some farmers have relied too much on the use of single herbicides like glyphosate to manage weeds in GM HT crops and this has contributed to the development of weed resistance. There are currently 28 weeds recognised as exhibiting resistance to glyphosate worldwide, of which several are not associated with glyphosate tolerant crops (www.weedscience.org). For example, there are currently 14 weeds recognised in the US as exhibiting resistance to glyphosate, of which two are not associated with glyphosate tolerant crops. In the US, the affected area is currently within a range of 20 percent-40 percent of the total area annually devoted to maize, cotton, canola, soybeans and sugar beet (the crops in which GM HT technology is used).

	Change in field EIQ impact (in terms of million field EIQ/ha units): developed countries	Change in field EIQ impact (in terms of million field EIQ/ha units): developing countries
GM HT soybeans	-4,773.9	-1,860.2
GM HT maize	-5,585.9	-438.8
GM HT cotton	-351.0	-109.3
GM HT canola	-509.1	0
GM IR maize	-1,574.4	-640.8
GM IR cotton	-805.5	-8,451.0
GM HT sugar beet	-2	0
Total	**-13,601.8**	**-11,520.1**

Table 7. GM crop environmental benefits from lower insecticide and herbicide use 1996-2012: developing versus developed countries

In recent years, there has also been a growing consensus among weed scientists of a need for changes in the weed management programmes in GM HT crops, because of the evolution of these weeds towards populations that are resistant to glyphosate. Growers of GM HT crops are increasingly being advised to be more proactive and include other herbicides (with different and complementary modes of action) in combination with glyphosate in their integrated weed management systems, even where instances of weed resistance to glyphosate have not been found.

This proactive, diversified approach to weed management is the principal strategy for avoiding the emergence of herbicide resistant weeds in GM HT crops. It is also the main way of tackling weed resistance in conventional crops. A proactive weed management programme also generally requires less herbicide, has a better environmental profile and is more economical than a reactive weed management programme.

At the macro level, the adoption of both reactive and proactive weed management programmes in GM HT crops has already begun to influence the mix, total amount and overall environmental profile of herbicides applied to GM HT soybeans, cotton, maize and canola and this is reflected in the data presented in this paper.

IMPACT ON GREENHOUSE GAS (GHG) EMISSIONS

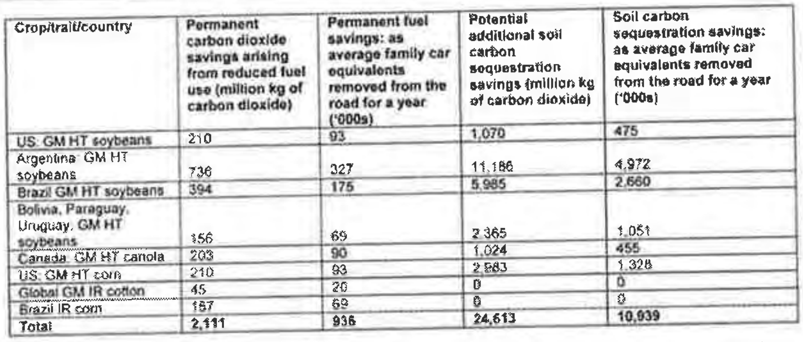
The scope for GM crops contributing to lower levels of GHG emissions comes from two principal sources:

- Reduced fuel use from less frequent herbicide or insecticide applications and a reduction in the energy use in soil cultivation. The fuel savings associated with making fewer spray runs (relative to conventional crops) and the switch to conservation, reduced and no-till farming systems, have resulted in permanent savings in carbon dioxide emissions. In 2012 this amounted to about 2,111 million kg (arising from reduced fuel use of 791 million litres). Over the period 1996 to 2012 the cumulative permanent reduction in fuel use is estimated at 16,736 million kg of carbon dioxide (arising from reduced fuel use of 6,268 million litres);
- The use of 'no-till' and 'reduced-till' (4) farming systems. These production systems have increased significantly with the adoption of GM HT crops because the GM HT technology has improved growers ability to control competing weeds, reducing the need to rely on soil cultivation and seed-bed preparation as means to getting good levels of weed control. As a result, tractor fuel use for tillage is reduced, soil quality is enhanced and levels of soil erosion cut. In turn more carbon remains in the soil and this leads to lower GHG emissions. Based on savings arising from the rapid adoption of no till/reduced tillage farming systems in North and South America, an extra 6,706 million kg of soil carbon is estimated to have been sequestered in 2012 (equivalent to 24,613 million tonnes of carbon dioxide that has not been released into the global atmosphere). Cumulatively, the amount of carbon sequestered may be higher than these estimates due to year-on-year benefits to soil quality; however it is equally likely that the total cumulative soil sequestration gains have been lower because only a proportion of the crop area will have remained in no-till and reduced tillage. It is, nevertheless, not possible to confidently estimate cumulative soil sequestration gains that take into account reversions to conventional tillage because of a lack of data. Consequently, our estimate of 203,560 million tonnes of carbon dioxide not released into the atmosphere should be treated with caution.

Placing these carbon sequestration benefits within the context of the carbon emissions from cars, Table 8 shows that:

- In 2012, the permanent carbon dioxide savings from reduced fuel use were the equivalent of removing 0.94 million cars from the road;
- The additional probable soil carbon sequestration gains in 2012 were equivalent to removing 10.94 million cars from the roads;
- In total, in 2012, the combined GM crop-related carbon dioxide emission savings from reduced fuel use and additional soil carbon sequestration were equal to the removal from the roads of 11.88 million cars, equivalent to 41.38 percent of all registered cars in the United Kingdom;
- It is not possible to confidently estimate the probable soil

carbon sequestration gains since 1996. If the entire GM HT crop in reduced or no tillage agriculture during the last seventeen years had remained in permanent reduced/no tillage then this would have resulted in a carbon dioxide saving of 203,560 million kg, equivalent to taking 90.5 million cars off the road. This is, however, a maximum possibility and the actual levels of carbon dioxide reduction are likely to be lower.



Crop/trait/country	Permanent carbon dioxide savings arising from reduced fuel use (million kg of carbon dioxide)	Permanent fuel savings: as average family car equivalents removed from the road for a year ('000s)	Potential additional soil carbon sequestration savings (million kg of carbon dioxide)	Soil carbon sequestration savings: as average family car equivalents removed from the road for a year ('000s)
US: GM HT soybeans	210	93	1,070	475
Argentina: GM HT soybeans	736	327	11,186	4,972
Brazil GM HT soybeans	394	175	5,985	2,660
Bolivia, Paraguay, Uruguay, GM HT soybeans	156	69	2,365	1,051
Canada: GM HT canola	203	90	1,024	455
US: GM HT corn	210	93	2,883	1,328
Global GM IR cotton	45	20	0	0
Brazil IR corn	157	69	0	0
Total	**2,111**	**936**	**24,613**	**10,939**

Notes: Assumption: an average family car produces 150 grams of carbon dioxide per km. A car does an average of 15,000 km/year and therefore produces 2,250 kg of carbon dioxide/year

Table 6 Context of carbon sequestration impact 2012: car equivalents

CONCLUDING COMMENTS

Crop biotechnology has, to date, delivered several specific agronomic traits that have overcome a number of production constraints for many farmers. This has resulted in improved productivity and profitability for the 17.3 million adopting farmers who have applied the technology to 160 million hectares in 2012.

During the last seventeen years, this technology has made important positive socio-economic and environmental contributions. These have arisen even though only a limited range of GM agronomic traits have so far been commercialised, in a small range of crops.

The crop biotechnology has delivered economic and environmental gains through a combination of their inherent technical advances and the role of the technology in the facilitation and evolution of more cost effective and environmentally friendly farming practices. More specifically:

- The gains from the GM IR traits have mostly been delivered directly from the technology (yield improvements, reduced production risk and decreased use of insecticides). Thus farmers (mostly in developing countries) have been able to both improve their productivity and economic returns, whilst also practising more environmentally-friendly farming methods;
- The gains from GM HT traits have come from a combination of direct benefits (mostly cost reductions to the farmer) and the facilitation of changes in farming systems. Thus, GM HT technology (especially in soybeans) has played an important role in enabling farmers to capitalise on the availability of a low cost, broad-spectrum herbicide (glyphosate) and, in turn, facilitated the move away from conventional to low/no-tillage production systems in both North and South America. This change in production system has made additional positive economic contributions to farmers (and the wider economy) and delivered important environmental benefits, notably reduced levels of GHG emissions (from reduced tractor fuel use and additional soil carbon sequestration);
- Both IR and HT traits have made important contributions to increasing world production levels of soybeans, corn, cotton and canola.
- In relation to GM HT crops, however, over reliance on the use of glyphosate by some farmers, in some regions, has contributed to the development of weed resistance. As a result, farmers are increasingly adopting a mix of reactive and proactive weed management strategies incorporating a mix of herbicides. Despite this, the overall environmental and economic gain from the use of GM crops has been, and continues to be, substantial.

Overall, there is a considerable body of evidence, in peer reviewed literature, and summarised in this paper, that quantifies the positive economic and environmental impacts of crop biotechnology. Readers are encouraged to read the peer reviewed papers cited in the references section of the main report this summary is taken from, and the many others who have published on this subject, and to draw their own conclusions.

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REFERENCES AND NOTES

1. The total number of reference sources used totals about 150, most of which are from peer reviewed journals
2. The cost of the technology accrues to the seed supply chain including sellers of seed to farmers, seed multipliers, plant breeders, distributors and the GM technology providers
3. This reflects the very good levels of *Heliothis/Helicoverpa* (boll and bud worm pests) pest control previously obtained with intensive insecticide use. The main benefit and reason for adoption of this technology in Australia has arisen from significant cost savings (on insecticides) and the associated environmental gains from reduced insecticide use
4. No-till farming means that the ground is not ploughed at all, while reduced tillage means that the ground is disturbed less than it would be with traditional tillage systems. For example, under a no-till farming system, soybean seeds are planted through the organic material that is left over from a previous crop such as corn, cotton or wheat

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LETTER

Changes in environmental impacts of major crops in the US

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Supplementary material for this article is available online

Abstract

As with life cycle assessment (LCA) studies in general, agricultural LCAs often rely on static and outdated inventory data, but literature suggests that agricultural systems may be highly dynamic. Here, we applied life cycle impact assessment methods to investigate the trends and underlying drivers of changes in non-global environmental impacts of major crops in the US. The results show that the impact per hectare corn and cotton generated on the ecological health of freshwater systems decreased by about 50% in the last decade. This change is mainly due to the use of genetically modified (GM) crops, which has reduced the application of insecticides and relatively toxic herbicides such as atrazine. However, the freshwater ecotoxicity impact per hectare soybean production increased by 3-fold, mainly because the spread of an invasive species, soybean aphid, has resulted in an increasing use of insecticides. In comparison, other impact categories remained relatively stable. By evaluating the relative ecotoxicity potential of a large number of pesticides, our analysis offers new insight into the benefits associated with GM crops. Our study also implies that because different impact categories show different degrees of changes, it is worthwhile focusing on the rapidly changing categories when updating agricultural LCA databases under time and resource constraints.

Decreased toxicity to waterways

1. Introduction

Agriculture is essential for feeding a majority of the global population, but it has also been identified as one of the major drivers behind various global environmental degradations [1–3]. Due to a quintupling of global fertilizer use in the past decades, agriculture has greatly disturbed the global nitrogen and phosphorus cycles [4]. This results in a wide range of environmental issues from release of N_2O, formation of photochemical smog over large regions of earth, to accumulation of excessive nutrients in estuaries and costal oceans [3]. Agriculture dominates pesticide use [5], which contaminates surface and ground water and threatens human and ecological health [6, 7]. So also does agriculture dominate freshwater withdrawal worldwide [8], adding stresses where there are competing needs for water [9]. Despite the severity of existing environmental impacts of agriculture, the challenge of addressing them is compounded by increasing global food demand [10]. Continuous global population growth and spread of economic prosperity [11], mainly in developing countries, will likely drive the global food demand to double by 2050 [12].

Over the past decade, life cycle assessment (LCA) has been increasingly applied to agricultural and food products [13, 14], with a number of agricultural LCA databases developed worldwide recently [15–19]. LCA is a tool that quantifies products' environmental releases and resource use throughout the life cycle and evaluates the potential impacts they generate on human and ecological health [20]. Impact categories evaluated in LCA span a wide range, from global warming, ozone depletion, acidification, eutrophication, to ecotoxicity, human health cancer, and human health non-cancer [21]. Applications of LCA in agriculture include comparing the environmental performance of alternative products or technologies [22], such as organic versus conventional farming [23], and identifying hotspots and improvement opportunities [24]. In particular, LCA has played an active and important role in assessing the environmental benefits of bioenergy [25] and contributed to the making of public climate policies [26].

As with LCA studies in general, agricultural LCAs often rely on static and single-year inventory data with commonly 5–10 years of data age. In the Ecoinvent (version 2.2) database, for example, the data year for *US Corn Farming* is around 2005 and for *Swiss Corn Farming* is around 2000 [27]. Literature suggests, however, that agricultural systems may be highly dynamic due in part to the increasingly changing climate [28] and technological advances such as improved yield and energy efficiency [29]. These factors may bring about significant changes in the use of input materials and the yield of crops, hence significant changes in the environmental impacts. For example, direct energy inputs per ha corn produced in the US declined by about 40% between 1996 and 2005 and in the meantime corn yield increased by about 30% [30].

In this study, we seek to evaluate if ongoing changes in input use and structure of four major crops in the US might have resulted in significant changes in their environmental impacts over the past decade, focusing on regional issues such as eutrophication, acidification, and ecological toxicity. The crops studied are corn, soybean, wheat, and cotton, which together account for around 70% of total harvested area domestically [31]. The main objectives of the study are to understand the extent to which different environmental impacts might have changed and to identify major drivers behind such changes.

2. Materials and methods

2.1. Method

Following previous LCA studies [32–34] we analyzed the cradle-to-gate life cycle environmental impacts of 1 ton and 1 hectare (ha)-year of crop production. The system boundary covers both direct and supply chain environmental releases associated with crop cultivation and harvest. Direct releases, such as nutrient leaching and runoff, result from the use of agricultural inputs. Indirect environmental releases occur along the upstream supply chain, including those from production and transportation of agricultural inputs like synthetic fertilizers. In previous analyses [35, 36], we have identified direct environmental releases as the major source of the overall life-cycle impacts of crops, thus in this study our data collection and analysis efforts were focused on direct releases. For supply chain environmental releases, we used the Ecoinvent database (version 2.2) [27].

We began with collecting data on the use of agricultural inputs in different years, and then estimated associated environmental releases based on environmental statistics and models. The releases data compiled were next aggregated using characterization models from Life Cycle Impact Assessment (LCIA) [37] to quantify their relative magnitudes of environmental impact. Equation (1) summarizes this calculation:

$$E_{i,k} = \sum_j C_{i,j}\left(m^D_{j,k} + m^I_{j,k}\right), \tag{1}$$

where i denotes impact category, k crops, and j environmental releases. m^D and m^I represent direct and indirect environmental releases, respectively. And C represents characterization factors used to aggregate releases j into characterized environmental impact scores E.

A characterization factor in LCA reflects the potency of an environmental exchange relative to that of a reference exchange for a given impact category [38]. Global warming potentials, for example, are commonly used characterization factors in LCA for the impact category of climate change. Characterization factors used in this study are from the Tool for the Reduction and Assessment of Chemical and Other Environmental Impacts (TRACI) version 2.0 developed by the US Environmental Protection Agency [39]. As our study targeted non-global impacts, the impact categories selected from TRACI 2.0 are acidification (air), eutrophication (water), smog formation, freshwater ecotoxicity, and human health criteria (air), cancer, and non-cancer (e.g., reproductive, developmental, and neurotoxic effects). Tale S1 in the supporting information (SI) provides a detailed explanation of these impact categories. Categories excluded from TRACI 2.0 are global warming, ozone depletion, and eutrophication (air). We also included irrigation water use as an indicator of the stress crops place on water scarcity. We excluded water use embodied in other inputs than irrigation partly because of a mismatch between the data years for irrigation water and other inputs like fertilizers (see section 2.2) and partly because embodied water in agricultural inputs is generally negligible relative to irrigation water use [36, 40].

2.2. Data on agricultural inputs

Major agricultural inputs include fertilizers, pesticides, irrigation water, and energy [35]. Data on fertilizer and pesticide use are from the US Department of Agriculture (USDA) [41], which surveys farmers in top-producing states annually on a rotating basis (table 1). We selected the years with the largest number of states covered for each crop to best represent US national situations. We found that top-producing states were consistently surveyed in the years selected for each crop, which ensures comparability across years. For example, the same 19 states were covered for corn and they accounted for around 95% of total corn area harvested in each of the years selected. Similarly, the same 9, 19, and 15 states were covered for cotton, soybean, and wheat, and these stated accounted for around 92%, 96%, and 88% of total area harvested, respectively.

Irrigation water use data are from the Farm and Ranch Irrigation surveys conducted also by USDA

Table 1. Number of states surveyed by USDA between 2000 and 2012[a].

	2000	01	02	03	04	05	06	07	08	09	10	11	2012
Corn	18	**19**	7	18		**19**					**19**		
Cotton	**11**	7		**12**		9		**11**			7		
Soybean	18	7	**20**		11	17	**19**						**19**
Wheat													
Durum	**1**		1		**2**		2			**3**			2
Spring	**4**		3		**7**		6			**7**			4
Winter	**16**		10		**14**		14			**16**			13

[a] Values in bold indicate years selected for analysis for each crop.

Table 2. Estimation of direct environmental releases from agricultural inputs.

Sources	Environmental releases	Ref/note
Nitrogen input	NH_3 to air	[50, 51]
	NO_x to air	[52]
	N runoff and leaching	[46]
Phosphate fertilizers	P runoff and leaching	[46]
	Heavy metals to soil	[53, 54]
Pesticides	Emissions to air	[48, 55]
	Runoff and leaching	[48]
	Releases to soil	[48]
Farm equipment	NO_x, SO_x, $PM_{2.5}$, PM_{10}, CO	[45]
	Speciated VOCs	[57]

[42], and the most recent three surveys for 2002, 2007, and 2012 were used for our analysis. State-level energy use data were also compiled from the USDA [43], but the data are somewhat outdated as they reflect crops planted in late 1990s or early 2000s. USDA has unfortunately ceased to update such data for most crops except for corn, which were updated to the year 2005 [30]. On the other hand, farms have become more efficient in response to rise in fuel and fertilizer prices in the last decade [44]. For example, on-farm energy use in corn production reduced by >20% between 2001 and 2005 [30]. To reflect the trend of farm energy efficiency gains, we adopted the estimates from the widely used GREET model [45], which shows an efficiency increase of about 30% for corn and soybean growth over the last decade. Few studies exist on cotton and wheat on-farm energy change, thus we assumed a similar 30% efficiency gain for them over the timescale investigated. Details on all the inputs applied to each crop can be found in tables S2–S6 (SI). Note that we did not consider nitrogen from manure considering that it is generally small relative to other nitrogen sources [46], and we estimated nitrogen input from biological fixation for soybean (see SI).

2.3. Direct environmental releases

Building on our previous studies [35, 36], we estimated a large number of substances (>100) from the use of agricultural inputs based on emission factors from various models and references (see table 2). Most of the substances covered are pesticides and speciated volatile organic compounds (VOCs). Details on all emission factors compiled can be found in tables S7–S12 (SI). In the context of characterization method in LCIA, it is important to clearly define 'release' and 'compartment of initial release', so that appropriate fate, transport, and exposure models are applied to release figures. For pesticide application several approaches have been utilized in LCA literature and databases. The Ecoinvent (v2.2) database, for example, assumes that all pesticides applied are released to agricultural soils [27]. In contrast, the PestLCI model treats agricultural soils as part of the technosphere and views pesticides released from soil as pollution [47]. Berthoud *et al* [48] and others, on the other hand, view that pesticides are released to multiple compartments (i.e., air, soil, and water) at the point of application [35, 48, 49]. We adopted the third approach in this paper. Specifically, we used a pesticide's vapor pressure to approximate its air emissions [48], assumed a generic factor of 0.5% of the total applied for pesticides lost to water systems through runoff and leaching [48], and assumed the remaining fraction, capped at 85% of the total applied, for pesticides emitted to soil [48].

Last, the data we compiled are at the state level, but given our emphasis on the change of environmental impacts of US agriculture on average we aggregated the state-level results to present totals. We also aggregated the three different types of wheat (winter, spring durum, and spring other) into one 'wheat' by adding up their annual agricultural inputs and outputs. In deriving the impacts per ton crop produced, we followed previous studies [30, 58] and used 3-year average yield data to reduce annual variation caused by possible extreme weather such as droughts and floods. For example, 2001 impact per ton for corn was calculated by dividing 2001 impact per ha by the average corn yield of 2000, 2001, and 2002.

3. Results and discussion

3.1. Changes in environmental impacts of US major crops

Figures 1 and 2 present our main results; because irrigation data span a different time frame, irrigation results are presented in a separate figure. Numerical information underlying figure 1 can be found in table S13 (SI). The major finding of our analysis is that

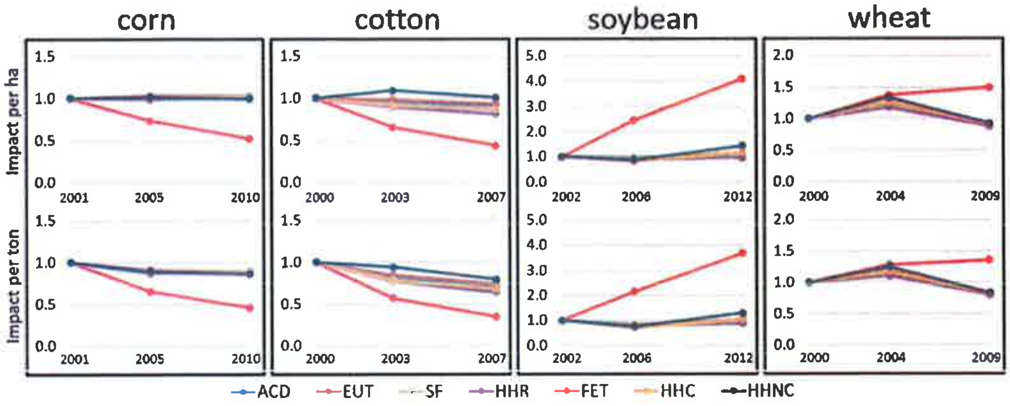

Figure 1. Changes in environmental impacts of US corn, cotton, soybean, and wheat. Impacts for different years were normalized to that for the base-year and expressed on the basis of impact per ha and per ton. ACD = acidification, EUT = eutrophication, SF = smog formation, HHR = human health respiratory, FET = freshwater ecotoxicity, HHC = human health cancer, and HHNC = human health non-cancer.

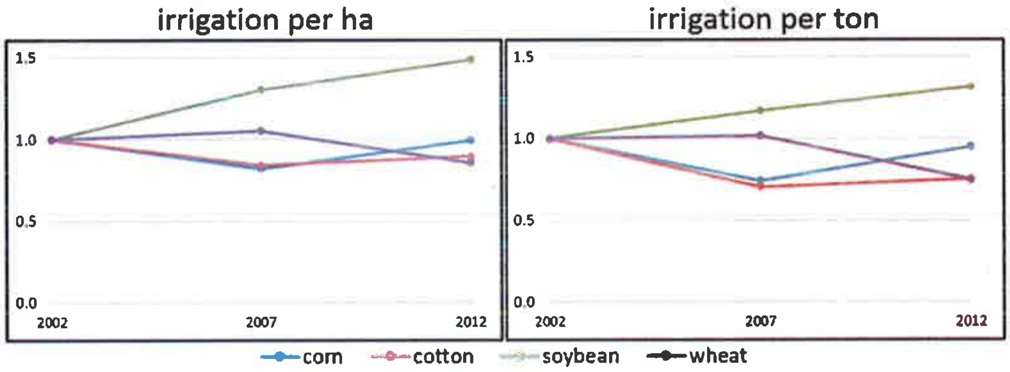

Figure 2. Changes in average on-farm irrigation water use per ha and per ton crop production, with results for different years normalized to that for 2002. Results for irrigation water per ha were derived from (*irrigation intensity for irrigated area* × *area irrigated*)/*total area harvested.*

freshwater ecotoxicity is the most dynamic of all impact categories, while the change is not unidirectional across the crops studied. We elaborate on this impact category, including its major contributors and probable drivers, in the next section (3.2). Here we focus on other impact categories.

Non-ecotoxicity categories were relatively stable over the past decade. Mostly, they changed 10–20% for each crop within the timescale studied. This is mainly because nutrient inputs—particularly nitrogen—are the major contributor for many of these impact categories. The use of nutrients results in both direct environmental releases (e.g., NH_3, NO_x, and nitrogen and phosphorus runoff) and indirect releases (e.g., such as NO_x) from the production of fertilizers. Also, fertilizers, particularly phosphate, introduce heavy metals into agricultural soils [54]. The total amount of nitrogen and phosphonate inputs remained largely unchanged for all of the crops over the periods investigated, and this is the main reason that most of the non-ecotoxicity impacts do not show a significant change.

For corn, soybean, and wheat, nutrients in general account for >75% of the non-ecotoxicity impacts (i.e., acidification, smog formation, eutrophication, human health cancer, non-cancer, and respiratory impacts). For cotton, energy use was intensive, about two times that of corn. As a result, nutrients account for around 50–80% for the non-ecotoxicity categories, while energy use contributes 25%, 40%, and 50% for acidification, smog formation, and human health respiratory impacts. For all crops, heavy metals introduced by phosphate fertilizers were identified to be the major contributor (60%–90%) to human health non-cancer impact.

As figure 2 reflects, changes in the average irrigation water use from 2002 to 2012 were also moderate for corn, cotton, and wheat, with variations <20% between 2002 and 2007 or between 2002 and 2012. In contrast, a noticeable upward trend can be observed for soybean. Average irrigation water use per ha soybean production increased by around 50%, from 180 m^3 in 2002 to 270 m^3 in 2012. On a per ton basis, the percentage increase is 30%, from 72 to 95 m^3, due to yield increase over the period. Behind this upward trend are several factors, including the slightly increasing irrigation intensity for irrigated area, but the major contributor is the growth in area irrigated (from 2.2 to 3.0 million ha) and its share in the total area harvested (from 7% to 10%). What led to the growth in soybean area irrigated is unclear, however, and further research is needed. Here, we offer a possible explanation. In the past 'ethanol decade', soybean and corn areas significantly expanded into other cropland and also grassland [59, 60]. Because such marginal land as grassland is on average not as fertile as existing corn or soybean fields [36], irrigation might have been applied to boost or maintain yield. Consequently, as total soybean and corn area expanded, so also did the area irrigated. In the case of corn, however, although area irrigated grew from 4.0 to 5.4 million ha between 2002 and 2012, its share in the total area harvested only slightly increased (from 14% to 15%). Additionally, irrigation intensity for area irrigated decreased from 3660 to 3350 $m^3\,ha^{-1}$. As a result, average irrigation use per ha or per ton corn production barely changed from 2002 to 2012.

3.2. Changes in freshwater ecotoxicity impact of US major crops

As reflected in figure 1, freshwater ecotoxicity impact per ha corn production decreased by around 50% from 2001 to 2010. Major contributors include reduced use of herbicides *atrazine* and *acetochlor*, and of insecticides *terbufos*, *dimethenamid*, and, especially, *chlorpyrifos* (figure 3). The downward trend is likely due to the continuous expansion of herbicide resistant (HR) and insect-resistant corn, particularly *glyphosate* tolerant and *Bacillus thuringiensis* (*Bt*) corn. Since its introduction in 1996, HR corn has now expanded to over 70% of cornfields [61], resulting in increasing use of *glyphosate* compounds in place of conventional herbicides like *atrazine* and *acetocholor*. In fact, *glyphosate* and related compounds had gradually surpassed *atrazine* and other herbicides over the past decade to become the most commonly applied pesticide [53]. As *glyphosate* compounds are relatively less toxic to ecosystems compared with the replaced herbicides like *atrazine* and *acetochlor* [62], the overall ecotoxicity impact of corn attributable to herbicides decreased moderately between 2001 and 2010. Meanwhile, *Bt* corn has also dominated US cornfields now [61], offering both economic and environmental benefits by protecting yield and reducing handling and use of insecticides [63]. This likely further contributed to the downward trend of corn's freshwater ecotoxicity impact.

Similar to corn, the freshwater ecotoxicity impact per ha cotton production decreased by 60% from 2000 to 2007, due to the reduced use of *chlorpyrifos*, *lambda-cyhalothrin*, and particularly *cyfluthrin* (figure 3). Application of *cyfluthrin* reduced from 11 g ha^{-1} in 2000 to 4 g ha^{-1} in 2007. Similar to corn, the downward trend in cotton's freshwater ecotoxicity impact was attributable to the expansion of HR and *Bt* varieties, which are now planted on 95% and 75% of US cotton fields respectively [61]. Our result on decreasing freshwater ecotoxicity impact of corn and cotton due to changes in pesticide use and patterns reinforces previous findings [63–65].

Unlike corn and cotton, soybean's freshwater ecotoxicity impact quintupled between 2002 and 2012. HR soybean has also expanded dramatically in the US, now planted on 95% of soybean fields [61]. Along with the expansion, application of *glyphosate* compounds per ha increased by over 60% between 2002 and 2012, and now they account for 80% of total pesticides applied in soybean growth. However, the benefits of HR soybean seem to have been entirely offset by the increasing use of insecticides *lambda-cyhalothrin*, *cyfluthrin*, and *chlorpyrifos* (figure 3). This is due to the invasion of soybean aphid, a species native to eastern Asia and first detected in North America in 2000, and application of insecticides has been the primary means of pest management [66]. Since its first detection, soybean aphid had rapidly spread to 30 states in the US by 2009 and become a major source of economic loss in soybean production [67]. As a result, the total quantity of insecticides applied to soybean quadrupled between 2002 and 2012, resulting in a 3-fold increase in soybean's freshwater ecotoxicity impact.

The freshwater ecotoxicity impact of wheat increased by about 40% from 2000 to 2009, attributable partly to increased use of several insecticides including *chlorpyrifos*, *cyfluthrin*, *beta-cyfluthrin*, and *lambda-cyhalothrin*. Also, pesticide application rate in general increased from 0.45 kg ha^{-1} in 2000 to 0.88 kg ha^{-1} in 2009. Unlike the other major crops, however, there is not a clear explanation for the upward trend. One possible reason may be the growing resistance of pests as a result of increasing pesticide use. Further research is needed in this area.

3.3. Sensitivity analyses

We conducted sensitivity analysis to test the robustness of the changes in freshwater ecotoxicity impact, considering that it is our major finding and that large uncertainty is involved in the estimation of pesticide releases and assessment of their ecotoxicity impact [62, 68, 69]. First, the proportion in which pesticides are emitted to water systems was identified as the major contributor to crops' freshwater ecotoxicity. Literature also shows it may vary greatly, from 5% [56] to 0.1% or even less [49, 68] (0.5% used in this study). We thus built three scenarios to test the sensitivity of the ecotoxicity result to different leaching and runoff rates. Additionally, we tested the sensitivity of the trends to other analytical approaches to pesticide releases (see section 2.3), with one assuming all

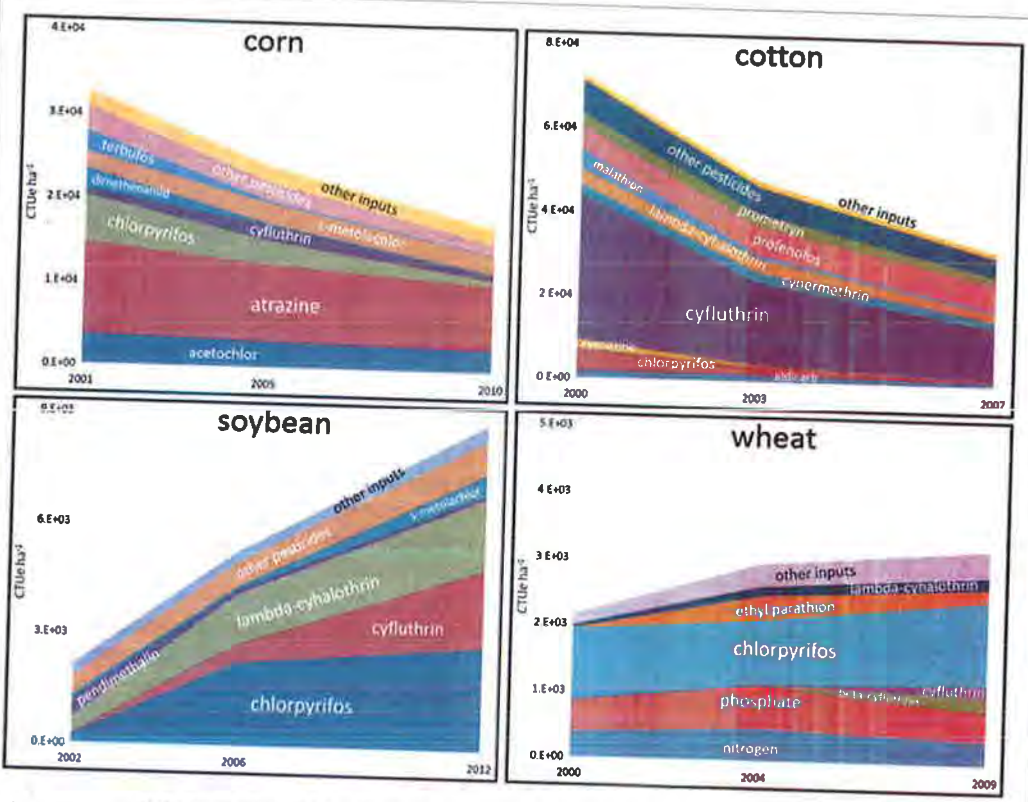

Figure 3. Changes in the composition of the cradle-to-gate life cycle freshwater ecotoxicity impact per ha corn, cotton, soybean, and wheat production over the past decade, expressed in comparative toxic units (CTU), which is a measure of the potentially affected fraction of species integrated over time and volume per unit mass of a chemical emitted.

pesticides to remain in soils and the other excluding the impact of pesticides on agricultural soils. All five scenarios are presented in figure 4, which reinforces the trends identified of freshwater ecotoxicity impact regardless of different runoff and leaching rates or different analytical approaches to pesticide releases.

Second, impact assessment of freshwater ecotoxicity is also highly uncertain, with the uncertainty range for TRACI 2.0 likely being 1–2 orders of magnitude [62]. However, detailed information on the distribution of each characterization factor is not available yet, thus a full uncertainty analysis is not feasible at this stage. To further test the robustness of the ecotoxicity results, we applied two other characterization models (i.e., IMPACT 2002+ and CML 2001) [70, 71] to evaluate the aquatic ecotoxicity impact of pesticide releases. For corn, cotton, and soybean, the other two models confirm the directionality of the changes but generally show a lower magnitude of change (figure 5). This is due in part to differences in the number of pesticides covered by the three models and in part to differences in the relative ecotoxicity potential they assign to each pesticide. Generally, IMPACT 2002+ and CML 2001 cover a smaller number of pesticides than TRACI 2.0, thus they may not capture all the changes in pesticide use and patterns that are captured by TRACI 2.0. For wheat, however, the results from the three characterization models disagree with regard to the directionality as well as the magnitude of changes (see SI). A detailed comparison, together with contribution analysis, is provided in the SI.

4. Conclusions

In this study, we evaluated several non-global environmental impacts of US corn, cotton, soybean, and wheat, and analyzed how they changed in the past decade. Due likely to the increasing adoption of genetically modified (GM) varieties, freshwater ecotoxicity impact per ha corn production declined by around 50% from 2001 to 2010 and per ha cotton production declined by 60% from 2000 to 2007. Due to the invasion of alien species (aphid) and increasing use of insecticides, freshwater ecotoxicity impact per ha soybean production increased by 3-fold from 2002 to 2012. In the meantime, on-farm irrigation water use per ha soybean harvested increased by about 50%. In comparison, other non-global impacts were relatively stable.

The major implication of our study is that identifying the underlying drivers of the dynamical mechanisms in agricultural systems would be essential for making informed agricultural decisions and policies, prioritizing LCA data update needs, and interpreting

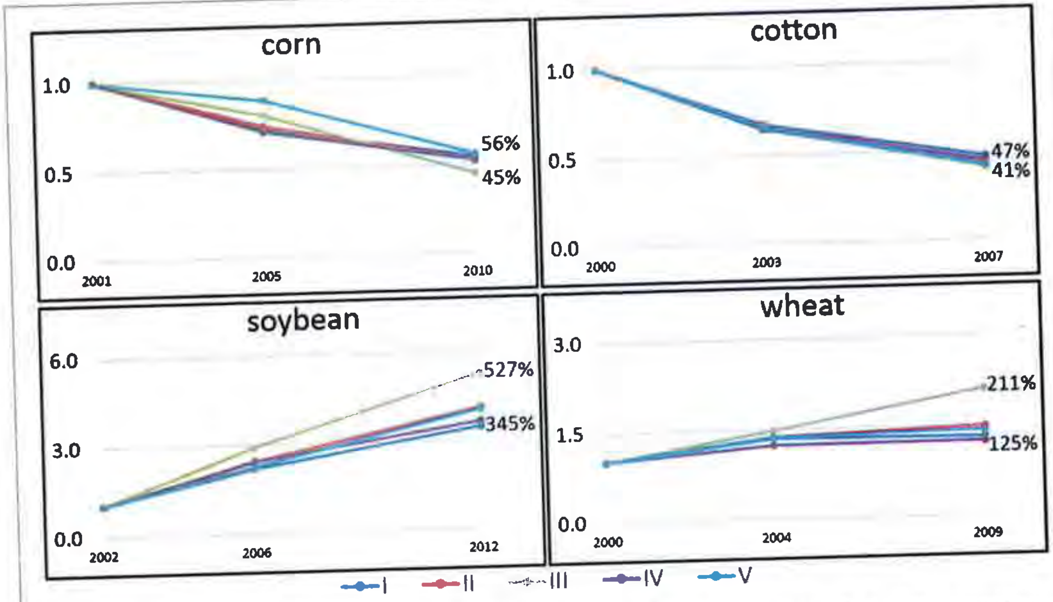

Figure 4. Changes in freshwater ecotoxicity impact per ha crop production based on different scenarios reflecting different pesticide runoff and leaching rates and approaches to pesticide releases. Results for different years were normalized to that for the base-year. Shown in each panel are maximal and minimal ratios, as an indicator of the variation of the scenarios tested. Scenario I = low runoff and leaching rate (0.1%); II = moderate runoff and leaching rate (0.5%, adopted in this study); III = high runoff and leaching rate (5%); IV = pesticides assumed to remain all in soil (100%); V = pesticides to soil considered as part of the technosphere and excluded from the overall ecotoxicity impact (with moderate runoff and leaching rate (0.5%) and estimation of pesticides to air based on their vapor pressure).

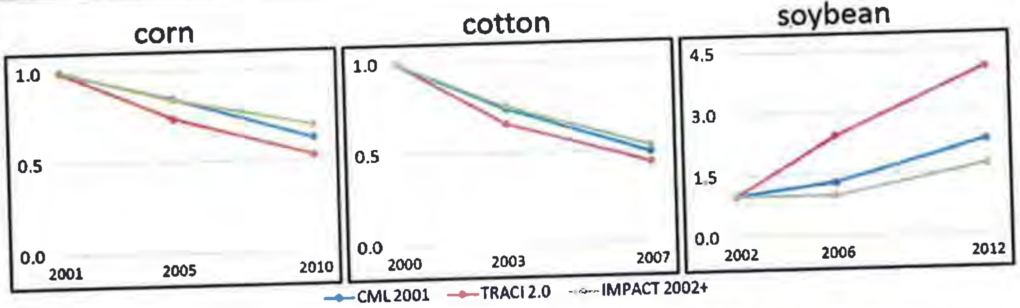

Figure 5. Changes in freshwater ecotoxicity impact per ha crop production using different LCIA characterization models, with a moderate runoff and leaching rate (i.e., 0.5%) assumed. Results for different years were normalized to that for the base-year.

LCA results. By evaluating the relative ecotoxicity potential of a large number of pesticides, we found that the use of GM crops have contributed to significant declines in corn and cotton's freshwater ecotoxicity impact. This finding provides an opportunity for better assessing the tradeoffs between the potential impacts of GM and conventional crops, as opposed to comparisons based mainly on the total quantity of pesticides applied [61]. Additionally, our results suggest that updates on agricultural inventory data can be done selectively, with regular updates needed for impact categories that are highly dynamic, such as pesticide related ecotoxicity. Studies relying on single-year and outdated data may inaccurately portray a crop's ecotoxicity impact; even just a few years of data age may substantially under or overestimate the ecotoxicity impact. This also implies that we should exercise caution when interpreting an LCA study in which ecotoxicity impact of agricultural processes plays an important role in the overall conclusion. Broadly, our study highlights the importance of understanding the dynamics in the input and output structure of a process or a technology in LCA [72, 73].

The focus of our study was to evaluate how environmental impacts of agriculture might have changed in the past decade. Our results that show decreasing freshwater ecotoxicity impacts for corn and cotton are not intended to prove that GM crops are overall more ecologically friendly than conventional crops. Other impacts of GM crops that could not have been evaluated due to the limitations of the current LCIA methods should also be taken into consideration in such comparisons. Current LCIA methods, for example, are not able to properly evaluate potential adverse effects of *Bt* toxin on populations of non-target species and elevated risk of species invasiveness through genetic modifications [74]. In addition, it should be noted that the trend of decreasing ecotoxicity impact is unlikely to continue for cotton and corn. Due to the dominant use of HR and *Bt* crops, pests and weeds have evolved to be increasingly resistant [75, 76]. As a result, farmers may need to resort to earlier pest control practices that rely more on conventional pesticides, hence increasing crops' freshwater ecotoxicity impact. Nevertheless, the dynamics of pest management, and associated ecological impacts, further corroborates the importance of understanding the dynamics of agricultural systems.

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Review article

The role of transgenic crops in sustainable development

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Summary

The concept of sustainable development forms the basis for a wide variety of international and national policy making. World population continues to expand at about 80 M people per year, while the demand for natural resources continues to escalate. Important policies, treaties and goals underpin the notion of sustainable development. In this paper, we discuss and evaluate a range of scientific literature pertaining to the use of transgenic crops in meeting sustainable development goals. It is concluded that a considerable body of evidence has accrued since the first commercial growing of transgenic crops, which suggests that they can contribute in all three traditional pillars of sustainability, i.e. economically, environmentally and socially. Management of herbicide-tolerant and insect-resistant transgenic crops to minimize the risk of weeds and pests developing resistance is discussed, together with the associated concern about the risk of loss of biodiversity. As the world population continues to rise, the evidence reviewed here suggests it would be unwise to ignore transgenic crops as one of the tools that can help meet aspirations for increasingly sustainable global development.

Introduction

Sustainable development permeates policy and action at the international, national and local level. Although the term sustainability has been used for several centuries, the unique relationship between the environment and societal actions was popularized by the book Silent Spring written in 1962 by Rachel Carson. The relationship between environment, economy and development has since grown in importance. The establishment of the International Institute for Environment and Development, the First Earth Day and the publication of the controversial 'Limits to Growth' (Club of Rome, 1972) all took place in the early 1970s. The World Watch Institute was established in 1975 and since 1984 has published annually the 'State of the World' reports. In 1980, the International Union for Conservation of Nature (IUCN) published its World Conservation Strategy with a section entitled 'toward sustainable development', which highlighted strong links between habitat destruction and poverty, population increase, social inequity and trade. The release of 'Our Common Future' in 1987, commonly known as the Brundtland report, brought the concept of sustainable development more widely into the public arena. Growing concerns about climate change led to the formation of the Intergovernmental Panel on Climate Change (IPCC) in 1988 and further international promises and conventions followed at both the 1992 (Rio de Janeiro) and 2002 (Johannesburg) summits. The Millennium Development Goals (MDGs) re-enforced a global desire to tackle the key sustainable development challenges related to growing population, poverty, hunger, health, damage and over exploitation of natural resources and biodiversity and concerns about the rate and severity of climate change. The recent substantive report 'Agriculture at a Crossroads' (IAASTD, 2009) noted, perhaps not surprisingly, that agricultural knowledge, science and technology are fundamental to meeting the MDGs, particularly related to poverty and livelihoods, although the report notes the general polarization in positions that individuals, organizations and indeed Governments adopt with respect to transgenic crops.

In 2009, the world population was 6.8 billion, and by 2025, the Population Reference Bureau expect it to increase to 8.1 billion (PRB, 2009). By 2050, it is predicted that population will stabilize at just over 9 BN (UN Population Council, 2003). Thus, in the next 40 years, the world population is likely to grow by a further 37%. FAO estimated that 1.02 billion people were undernourished worldwide in 2009 (FAO, 2009). Paradoxically, an almost equal number suffer with obesity with the potential for associated diabetes and metabolic disease. With an increasing world population, the desire for economic development and increasing urbanization, the global demand for food will continue to grow. At the same time, climate change is leading to production uncertainties, and the reliance on fossil fuels in food production systems is of increasing concern. (RSC, 2009; Karlsson, 2009; UNCOD, 2008).

Table 1 Global area of biotech crops in 2008 by country (after James, 2009)

Country	Area (Mha)	Biotech crops
USA	64.0	Soya bean, maize, cotton, rape, squash, papaya, alfalfa, sugar beet
Brazil	21.4	Soya bean, maize, cotton
Argentina	21.3	Soya bean, maize, cotton
India	8.4	Cotton
Canada	8.2	Rape, maize, soya bean, sugar beet
China	3.7	Cotton, tomato, poplar, papaya, sweet pepper
Paraguay	2.2	Soya bean
South Africa	2.1	Maize, soya bean, cotton
Uruguay	0.8	Soya bean, maize
Bolivia	0.8	Soya bean
Philippines	0.5	Maize
Australia	0.2	Cotton, rape, carnation
Burkina Faso	0.1	Cotton
Mexico	0.1	Cotton, soya bean
Spain	0.1	Maize
Chile	<0.1	Maize, soya bean, rape
Colombia	<0.1	Cotton, carnation
Honduras	<0.1	Maize
Czech Republic	<0.1	Maize
Romania	<0.1	Maize
Portugal	<0.1	Maize
Poland	<0.1	Maize
Costa Rica	<0.1	Cotton, soya bean
Slovakia	<0.1	Maize
Egypt	<0.1	Maize

Against this backcloth, a range of transgenic crops have been developed, and a few are now being grown in many parts of the world; so far the crops are either herbicide-tolerant, giving farmers greater choice in crop management, or insect-resistant, reducing the need for spraying with pesticides. A variety of novel transgenic crops, some offering nutritional benefits and others that are tolerant of drought and other forms of stress, or higher yielding, are at advanced stages of testing. As well as performance testing, they are being tested from the point of view of environmental impact and biosecurity. Data from the biotech industry suggest that since wide-scale planting started in 1996, the area of transgenic crops grown globally has increased from 2 to 134 Mha in 2009 (James, 2009), of which 131 Mha are grown in eight countries: USA, Brazil, Argentina, India, Canada, China, Paraguay and South Africa. Other countries that include Uruguay, Bolivia, Philippines, Australia, Mexico, Spain, Chile, Columbia, Honduras, Bukina Faso, Czech Republic, Romania, Portugal, Germany, Slovakia and Poland grow between <0.1 and 0.8 Mha (Table 1). Currently, these crops are grown by 13.3 million farmers, who are attracted by the potential to reduce input costs as a mechanism for maintaining margins rather than expecting increases in yields *per se*. However, it is important to note that the largest numbers of farmers growing transgenic crops are small-scale producers (12.3 million of the 13.3 million growers of biotech crops in 2008 were small and resource-poor farmers), particularly in India, China, South Africa and Philippines (James, 2008). The principal transgenic crops are soya bean, maize, cotton and canola, which are modified for agronomic input traits such as herbicide tolerance (HT) and or insect resistance (*Bacillus thuringiensis-Bt*). On a global basis, transgenic crops are 77%, 26% and 49% of the total soya bean, maize and cotton areas, respectively (James, 2009). Currently, 60% of all transgenic crops grown have the single trait of HT. However, there has been a marked increase in use of transgenic crops containing stacked traits (HT and *Bt*), and these now contribute a higher proportion of the total area than crops modified for just *Bt*. Between 2007 and 2008, the area of transgenic maize grown in the USA with three inserted traits increased from 28% to 48% (James, 2008), and this trend is likely to increase. Recent work has focussed on the use of biotechnology to produce abiotic stress-tolerant and nutritionally enhanced food and feed with a range of new events being predicted by 2015 (Newell-McGloughlin, 2008; Stein and Rodriguez-Cerezo, 2009).

Despite the growth and use of transgenic crops in many areas of the world, some governments, organizations and individuals still hesitate to acknowledge that transgenic crops provide economic and environmental benefits that are unobtainable in a timely manner via non-transgenic advances in plant breeding. For example, Binimelis *et al.* (2009) reported the appearance in Argentina of a growing number of glyphosate-tolerant or glyphosate-resistant weeds, with socio-environmental consequences apart from the loss of productivity. Hall and Moran (2006) described some of the organizations that believe that there are unacceptable risks associated with the release of transgenic crops, and some scientists have expressed caution about specific issues such as disturbance of nitrogen balance in soils (Gurian-Sherman and Gurwick, 2009). A balanced view is presented by the UK Royal Society (2009): 'The reality is that there is no technological panacea for the global challenge of sustainable and secure food production…new crop varieties and appropriate agro-ecological practices are both needed'.

The overall thesis of the paper is that if the growing world population is to be adequately fed, both in terms of quantity and quality, without further compromising the environmental services that the planet provides, then transgenic crops are a potential 'tool' giving options for ongoing sustainable development. This paper considers the contribution of transgenic crops in relation to the three recognized pillars of sustainability (economic, environmental and social), and where possible makes links to specific sustainable development goals and targets. In the Economic dimension, we examine the evidence that yield is maintained or enhanced relative to non-transgenic crops and that inputs are reduced; we also note the sharing of economic benefit between suppliers, farmers and consumers. In the Environmental dimension, we look first at the long-term environmental prospects for maintaining soil quality, reducing greenhouse gas emissions and conserving water supplies; Environmental dimension continues with environmental issues specific to transgenic crops: coexistence, biodiversity and emergence of resistance. In the Social dimension, we review implications for human health and nutrition before discussing the overall implications for sustainable development.

Economic dimension

The aim of the first of the eight United Nations Millennium Development Goals (UN, 2009) is to eradicate extreme poverty and hunger. As many of the poorest peoples and countries in the world are highly reliant on agriculture, then it is likely that developments in crop and animal husbandry will have a direct impact on achieving this goal (DFID, 2005) and lead to improved economic conditions. The eight goals are claimed to represent a partnership between developed and developing countries, which is conducive to both development and the elimination of poverty, and indeed Goal 8 relates directly to Global Partnerships for Development. An example of such a partnership is the initiative between the Bill and Melinda Gates and the Howard G Buffet Foundations who have provided US$ 50 million to research centres in Africa to help develop drought-tolerant crops. Although in a different economic context, farm incomes in developed countries have also been squeezed by rising input costs and volatile commodity prices and thus farmers are carefully evaluating their production systems including the use of transgenic crops to either reduce input costs and or increase production or product value/quality. In the following sections, the effects of transgenic crops are considered in relation to crop yield, inputs such as pesticides and their effects on overall profitability.

Yield impacts

The release of the first transgenic events with insect resistance (*Bt*) or HT (Schuler *et al.*, 1998; Bates *et al.*, 2005) was not engineered to increase yield directly, but experience has shown that, by reducing losses from pests and weed competition, these varieties have in many cases delivered increased yields when compared with conventional crops.

For *Bt* cotton, Fernandez-Cornejo and Caswell (2006) reported that the increases in cotton yields in the Southeast United States were associated with the adoption of HT and *Bt* cotton in 1997. The same authors quote a 2001 US government survey data showing that maize yield was 9% higher for *Bt* maize than for conventional maize. Gianessi (2008) reported the outcome of a study in Mississippi over 3 years, in which *Bt* cotton produced higher lint yields and had an economic advantage when compared with conventional cotton varieties. Although the transgenic varieties in years two and three had greater costs associated with insect control, the economic advantage associated with the transgenic cotton for the 3 years was $82, $24 and $53 per acre, respectively, when compared with conventional cotton varieties.

In China, *Bt* cotton was first approved in 1997 and by 2004 accounted for 69% of cotton grown in China, with 100% adoption in Shandong province, where pest pressure was greatest (James, 2008). Approval came later in India, in 2002, but as early as 2006, India's *Bt* cotton area exceeded that of China, and in 2008 accounted for 80% of India's cotton output (James, 2009). Karihaloo & Kumar (2009) noted that between 2003–04 and 2006–07 cotton yields in India indicate a significant yield advantage of more than 30% with *Bt* cotton compared with conventional varieties with corresponding increase in farm income.

Yield enhancement varies depending on environment and the local intensity of pest and weed pressures. Commenting on yield increases obtained by *Bt* maize farmers in Spain, Gomez-Barbero *et al.* (2008) observed regional differences in yield between *Bt* and conventional maize ranging from −1.3% to +12.1%, with the yield advantage of *Bt* directly related to local pest pressure. They noted that *Bt* technology performed differently in the three regions studied, and this variability was explained by heterogeneity between farmers, differences in pest pressure, agro-ecological conditions and the fact that *Bt* technology may not yet have been introduced in varieties suitable for all regions.

Carpenter *et al.* (CAST, 2002) found that the trend in soya bean yields was continually upward through to 2001, a year in which 68% of the total soya bean area was planted with HT soya bean varieties. The study of Fernadez-Cornejo and McBride (2002) suggests that for HT soya bean, a 10% increase in adoption in the USA would lead to a 0.3% yield increase. At the same time, the yield effect seems to be compensated for by the higher seed prices as the authors found that a 10% increase in adoption would lead to no change in net returns on the farm, but the more recent data quoted above for the continuing increase in the numbers of farmers adopting HT soya bean suggest that farmers are finding sufficient benefits overall. Better results were obtained for HT corn where a 10% increase in adoption generated a 1.7% increase in yield and a 1.8% increase in net returns.

Commercial planting of HT soya beans in Romania between 1999 and 2008 was associated with an average increase in yields of 31% because of improved weed control, especially of difficult-to-control established weeds such as Johnson grass. A recent report on the sustainability of soya bean production in the USA (CAST, 2009) suggests that about 29 Mha of soya bean are grown each year in 31 states, covering about 22% of the total crop area of the United States. Of this, 92% is now glyphosate-resistant HT, and thus, it is essentially the 'conventional' growing system.

The Canola Council of Canada reported yield increases of up to 10% for transgenic compared with conventional varieties of canola. Direct comparison between mean yields of adopters versus non-adopters needs treating with caution as the adopters could be the more productive farmers anyway. HT Canola was grown commercially in Canada for the first time in 1997. Within 6 years of the transgenic varieties being available, over 90% of the area was HT Canola and the overall area of the crop grown had increased from 12 to 16 Mha. One of the main reasons for adoption was that HT canola is used as a 'cleaning crop'. In this way, the need for fallow is removed and farmers can have one more crop in the rotation. Phillips (2003) reported an economic benefit of C$ 28 per ha for HT over conventional. Gusta *et al.* (2010) suggested based on a survey of growers that this figure had increased to C$38 per ha.

These data suggest that across a range of agro-ecological zones, the four main transgenic crops have at worst been neutral in relation to yield and in many cases have increased yields.

Input impacts

Early transgenic events have been associated with improving the management of crops through pest resistance and/or weed control. This has often been associated with reduced pesticide use, or the use of cheaper pesticides with wider efficacy, thus having the potential to improve profitability. Qaim (2005), in a review of adoption of transgenic crops in developing countries, reported average pesticide savings between 33% and 77% for HT and insect-resistant (IR) events, commenting that the savings for HT soya beans are from the lower cost of glyphosate relative to other herbicides, while insecticide savings for *Bt* cotton are directly from reduction in quantity applied. Reporting in more detail, Qaim and Traxler (2005) noted savings of 24% in weed management costs in favour of HT soya bean when compared with conventional soya bean weed control programmes, commenting that glyphosate is usually cheaper than other herbicides. The benefits to Argentine farmers who had adopted HT soya beans was estimated to be $30 per ha based on a cost of the technology of $3 per ha, thus providing an additional margin of $27 per ha. The introduction of HT soya beans encouraged minimal tillage systems, which resulted in fewer tillage operations resulting in lower fuel input cost and reduced the time needed for harvesting, and consequently it has reduced labour and machinery costs by 14%.

For farmers in developing countries, Qaim reports that input savings alone outweigh the additional seed cost in all regions with high adoption rates, and in most cases, farm incomes are further enhanced by the improved yield because of more efficient control of crop losses.

As noted previously, farmers in developed countries, notably in the USA, pay more for HT soya bean seed than conventional seed. Bonny (2008) identifies the associated agro-economic effects that enable farmers in USA to offset this 'technology fee':

1. Ease of weed management using glyphosate as sole herbicide
2. Flexibility arising from longer period available for application
3. Reduced overall cost of herbicide treatments
4. Reduced risk of incomplete weeding
5. Easier crop rotation associated with less herbicide residue
6. Generally fewer herbicide treatments
7. Reduced labour and equipment costs
8. Opportunity for conservation tillage.

These advantages are offset by the cost of precautions to avoid build up glyphosate resistance, but the necessary precautions are now well understood. Responses to the build up of resistance in the context of HT soya bean production in Argentina were reported and discussed by Binimelis *et al.* (2009). Similarly, in commenting on the use of refuge areas as a strategy to delay the build up of insect resistance, Tabashnik (2008) noted that there had been a decade of resistance monitoring data for six major pests targeted by *Bt*, demonstrating the success of refuges; resistance had been detected in only one of the six pests and that only after 7–8 years. Seed suppliers have attempted to make provision of *refugia* a mandatory part of stewardship agreements with adopters particularly to comply with EU regulations, with only partial success. Strategies to minimize build up of resistance are discussed later in the paper.

It was noted at an early stage that transgenic crops have the potential to reduce the indirect application costs, such as reduced field operations and associated reductions in diesel usage (Phipps and Park, 2002). In the case study mentioned earlier of maize grown in Florida (Gianassi, 2008), there was a 79% reduction in insecticide use, and a corresponding $3.9 million per year increase in production value. The change in production costs was estimated to provide $1.3 million in net savings in insect control. Farmers in Florida would on average save $33 per ha. Gianessi further reports that in 2005, the use of HT soya beans was estimated to cost less than the effective alternative programmes by an average of $45 per ha, thus reducing farmer input costs by $1.17 billion on the USA's 26 Mha of HT maize.

The US National Centre for Food and Agricultural Policy (NCFAP) estimates that the cost advantage to the HT maize weed control programme in 2005 was $23.7 per ha in comparison with weed control programmes in conventional maize. Thus, with 11.3 Mha of HT maize planted in 2005, the aggregate net value to the US farmers of HT maize was estimated at $269 million. This figure has increased markedly as the area of HT maize has continued to increase.

In marked contrast with conventional canola crops in Canada where herbicide application rose by 29% between 1996 and 2000, the herbicide application rate in transgenic crops declined by 20%. Herbicide use per hectare in HT canola has remained consistently lower than conventional canola. The mean amount of herbicide applied in conventional canola from 1996 to 2000 was 0.69 kg/ha, which was significantly higher than the 0.34 kg/ha applied to HT canola (Brimner, 2004).

In addition to the above direct benefits, Beckie *et al.* (2006) reported that HT canola enabled Canadian farmers to plant earlier in the year, achieving higher yields from better utilization of snow-melt moisture and from reduced environmental stress during flowering. Early planting also introduced operational diversity, particularly in relation to weed management systems, which has lead to increases in overall economic performance (Gusta *et al.*, 2010).

Such changes in farming system with transgenic crops are common, and the glyphosate-resistant weed control package for soya beans has led to changes in rotation and fallowing practices. In Louisiana, conventional practice for many years has been to grow sugarcane for 3–5 years, followed by crop destruction and a fallow period when glyphosate is used to reduce Johnson grass levels. Research has shown that, instead of fallowing, the field can be planted with glyphosate-resistant soya beans, and the glyphosate usage will reduce the Johnson grass levels for the subsequent sugarcane crop while at the same time resulting in a profitable soya bean crop instead of a non-crop fallow period (Gianassi, 2008). Clewis and Wilcut (2007) also confirmed the economic advantage of weed management using strip tillage in transgenic cotton, compared with conventional crop and tillage systems. Their data showed that economically effective weed management can be obtained in both conventional and strip-tillage transgenic cotton production environments.

In relation to cotton in Argentina, Qaim *et al.* (2003) reported that *Bt* cotton could halve pesticide use while also increasing yield. However, Jost *et al.* (2008), considering the growth of transgenic cotton in Georgia, USA, suggested that although pesticide usage was reduced in transgenic crops, the overall economics when compared with conventional systems was not significantly different. It is also interesting to note that in villages in India, women earn more from *Bt* cotton as they traditionally do the picking and men do the spraying, the amount of which has been reduced because of the introduction of *Bt* cotton (Subramanian and Qaim, 2009). In addition, Raney (2006) has shown that even when allowing for the higher seed costs of transgenic varieties, the use of *Bt* cotton in Argentina, China, India, Mexico and South Africa increased yield of lint, revenue and profit and reduced pesticide costs.

More advanced transgenic cotton varieties such as Bollgard II, which contains two *Bt* genes and express two cry-proteins (Cry1Ac and Cry2Ab2), are now available and are becoming widely used. Gore *et al.* (2008) conducted experiments with two such varieties and confirmed that cotton yields suffer little damage even under extreme high pressure of bollworm infestation unlike those with a single gene insertion. Vitale *et al.* (2008) comments that experimental station results appear to be conservative in their assessment of Bollgard II because the observed pest densities were lower than that typically found under actual farming conditions.

In summary, the adoption of insect- and herbicide-tolerant varieties often leads to reductions in pesticide applications when compared to 'conventional systems', with resultant cost savings. Farmers will increasingly be able to purchase varieties with stacked traits to match specific agronomic issues they are facing (Stein and Rodriguez-Cerezo, 2009). The area of transgenic crops grown with stacked traits is increasing, and the use of such biotechnological innovations should lead to further reductions in pesticide use and increased yields.

Sharing of economic benefit

There has been considerable debate about the uptake and economics of transgenic crops in developing countries (Frow *et al.*, 2009; Sonnino *et al.*, 2009), although Brookes and Barfoot (2008) report that a common cost ratio applies across all the transgenic crops: that is, payments to the seed supply chain (including sellers of seed to farmers, seed multipliers, plant breeders, distributors and the transgenic technology provider) are typically about one-third of the net benefit. They provide an overview of the economic benefits for different countries between 1996 and 2007 (Table 2).

Table 2 Economic impact of transgenic crops: 1996–2007, US$M

Country	Cumulated economic benefit 1996–2007, US$M
United States	19789
Argentina	8184
China	6740
India	3181
Brazil	2933
Canada	1643

Adapted from Brookes and Barfoot (2009)

Extensive *ex post* studies of transgenic crop adoption have been conducted for *Bt* cotton in Argentina, China, India, Mexico and South Africa (Raney, 2006). Yield improvement, higher revenue and lower pesticide costs are widely reported for *Bt* cotton, producing in most cases significant net benefit after accounting for higher seed prices. Other large-scale transgenic crops include HT soya beans, grown in Argentina, Brazil and Paraguay. James (2009) reported that in 2009, about 77% of worldwide soya bean production was transgenic and that the cumulative benefits in Argentina between 1996 and 2005 were US$20 BN.

Overall, the evidence strongly suggests that in both developed and developing countries, the adoption of transgenic crops can increase the farmer's income. The increase in income to small-scale farmers in developing countries can have a direct impact on poverty alleviation and quality of life, a key component of sustainable development. Bennett *et al.* (2006) compared the performance of over 9000 *Bt* and non-*Bt* cotton farm plots in Maharashtra in India and reported that *Bt* cotton varieties had a significant positive impact on average yields and on the economic performance of cotton growers. However, they note that not all farmers had benefited from increased performance of *Bt* varieties because of regional variations in agro-climate conditions and thus yield. Bennett *et al.* (2006) reported similar results following a 3 year study in South Africa of resource-poor smallholder cotton farmers. Their results conclusively show that adopters of *Bt* cotton have benefited in terms of higher yields, lower pesticide use, less labour for pesticide application and substantially higher gross margins per hectare. They go on to note 'that the smallest producers are shown to have benefited from adoption of the *Bt* variety as much as, if not more than, larger producers.' This suggests that transgenic crops do have a key role to play in poverty alleviation and thus international development goals.

Environmental dimension

The MDGs are overarching in their nature, although Goal 7 refers specifically to environmental sustainability. This illustrates the recognition by the international community of the strong links between environment and economy and the fact that continued economic development and the state of the environment are very closely linked (Arrow *et al.*, 1995; IAASTD, 2009, UNDP-UNEP 2009). The most important comprehensive international plan of action is Agenda 21 (UNCED, 1992), which relates to all areas in which human's effect their environment. The following sections discuss how transgenic technology may have an impact on environmental sustainability.

Land use and soil quality

Within Agenda 21, there is a section on the conservation and management of resources for development. Managing fragile ecosystems by combating desertification and drought is a focus within this section. Desertification is a recognized worldwide environmental issue. The most recent action to tackle this issue resulted in the United Nations Convention to Combat Desertification in those countries experiencing serious drought and/or desertification, particularly in Africa (UNCCD, 2008). The aims of this convention are to combat desertification and through international partnerships to prepare long-term national action plans to link land use and livelihood to the target of sustainable development and to mitigate the effects of climate change, and UNCCD is the only legally binding convention focused on combating desertification.

The main mechanisms by which transgenic crops have contributed directly to land and soil quality is that they are conducive to minimum and no-till soil management techniques. These reduce the potential for soil erosion and increase the storage of organic matter in the soil, which will in turn help to retain soil moisture. Given an appropriate combination of herbicides and crops that are resistant to those herbicides, no or minimum or conservation tillage can be practiced, which reduces soil erosion and associated loading of pesticides, nutrients and sediments into the environment and decreases direct energy input required for crop production. However, it should be noted that no-till can lead to increases in both pesticide and fertilizer requirements, particularly in the initial years of adoption.

The use of HT canola in Canada is mainly because it allows the use of canola as a cleaning crop within the rotation. Thus, the need for fallow and mechanical weeding is removed, meaning that over the rotation, the overall crop productivity increases in relation to inputs such as chemicals, fertiliser and mechanization. Similarly, the American Soya bean Association strongly supports adoption of transgenic soya beans (Docket No. APHIS 2007-0019) and in particular describes the associated conservation tillage crop production methods as having decreased soil erosion because of wind and water by 90%, and greatly reduced consumption of fuel required for US soya bean production.

In relation to soil biological properties, studies with reduced tillage have shown that these systems achieved considerable success in enhancing soil quality and preventing soil erosion (Christoffoleti *et al.*, 2007) and that when HT crops were grown under these conditions, soils showed that HT maize and cotton maintained higher levels of soil organic carbon and nitrogen when compared with conventional crops (Christoffoleti *et al.*, 2008). Results from these studies indicate positive differences attributable to the interaction of conservation practices and glyphosate-resistant crop.

Crop residues are the primary source of soil carbon enrichment, and root exudates govern which organisms reside in the rhizosphere. Therefore, any change to the nature or quality of returned crop residues could modify the dynamics of the composition and activity of organisms in soil. It has been suggested that *Bt* crops may change the microbial dynamics, biodiversity and essential ecosystem functions in soil, because they usually produce insecticidal Cry proteins through all parts of the plant. It is therefore crucial that risk assessment studies on the commercial use of *Bt* crops consider the impacts on organisms in soil. However studies, reported from China by Liu *et al.* (2008), have shown that *Bt* rice has no adverse effect on rhizosphere soil microbial community composition and concluded that the Cry1Ab gene had no measurable adverse effect on the key microbial processes or microbial community composition.

Icoz and Stotsky (2008) reviewed the effect of *Bt* crops on soils. The review discusses the available data on the effects of Cry proteins on below-ground organisms, the fate of these proteins in soil, the techniques and indicators that are available to study these aspects. They conclude that the use of IR *Bt* crops, expressing highly specific *Bt* proteins, had no marked effects on woodlice, collembolans, mites, earthworms, nematodes, protozoa, and the activity of various soil enzymes and represented an opportunity to replace the use of broad-spectrum insecticides.

Linking directly to the issue of desertification, some of the transgenic events in the pipeline related to drought- and salt-tolerant varieties are likely to enable the cultivation of crops in areas where yields are currently low or indeed in areas where cultivations has been abandoned. The problems associated with soil salinization, which affects 20%–50% of the global irrigated farmland, have been reviewed by Geissler *et al.* (2008).

Slowing of deforestation and the designation of forests for biodiversity conservation is one of the targets of the MDGs. While the original transgenic events were not primarily designed to increase yield, yield increases have in many cases occurred. However, it is anticipated that in the medium term, events in the pipeline are likely to have more significant impact on yield, and this could lessen the pressure to further expand agricultural production into natural forest areas.

In summary, transgenic crops have enabled and encouraged some farmers to adopt conservation tillage techniques, thus reducing soil erosion and potentially improving soil quality through a gradual accumulation of organic material in the soil. Emerging technologies are likely to enhance the potential for cropping in arid and saline environments, potentially bringing degraded areas back into production. Drought is the most significant environmental stress in agriculture worldwide, and improving yield under drought conditions is a major goal of plant breeding. A review by Cattivelli *et al.* (2008) of improvements in drought tolerance considers the new insights into the complexity of plant mechanisms enabled by genomics, but there is still a large gap between yields in optimal and stress conditions. Minimizing the 'yield gap' and increasing yield stability under different stress conditions are of strategic importance in guaranteeing food for the future. In the longer-term modifications aimed more specifically at stabilizing yields in stressed environments and increasing yields in more productive regions may help to offset the demand for the conversion of further forested lands to arable production, this seeming an inevitable consequence of the expanding world population.

Greenhouse gases

The first major international treaty established to tackle the emission of greenhouse gases (GHG) was the United Nations Framework Convention on Climate Change (UNFCCC, 1998). The objective of this treaty was to achieve 'stabilization of greenhouse gas concentrations in the atmosphere at a low enough level to prevent dangerous anthropogenic interference with the climate system'. The recognition of the importance of legally binding targets led to the Kyoto Protocol, which required the developed countries to reduce greenhouse gas emissions to an average of 5.2% below their 1990 emissions levels by 2008–2012.

The use of transgenic crops has the potential to reduce GHG via several mechanisms. If less pesticide is required, then this will reduce emissions because of a reduction in emissions related to their manufacture. Lower rates of application will reduce the amount of fuel required, and if this is combined with lower levels of cultivation, for instance related to minimum tillage or no till, then GHG savings could be significant (Phipps and Park, 2002). Subsequent ISAAA reports have suggested significant savings in carbon equivalents. For instance in 2007, they estimated savings of 1.1 BN kg of CO_2 because of the usage of less sprays. However, they also estimated an additional saving of 13.1 BN kg CO_2 in cases where the use of herbicide-tolerant varieties had facilitated the use of min-till systems (ISAAA, 2009).

The UN Food and Agriculture Organization (FAO, 2008) have quantified the contribution of conservation tillage to carbon sequestration. They state that soil carbon sequestration during the first decade of adoption of best conservation agricultural practices is 1.8 tons CO_2 per hectare per year, with better cycling of nutrients and avoiding nutrient losses among the key benefits to farmers. Thus, in systems where transgenic crops enable wider use of conservation tillage systems, this is likely to be accompanied by reductions in GHG emissions.

Glover *et al.* (2008) reviewed the relevance of biotechnology in the context of climate change. They note that the agricultural sector accounts for 16%–18% of Australia's net greenhouse gas emissions, which includes nitrous oxide (primarily from fertiliser applications), methane (primarily from livestock) and carbon dioxide. As a net emitter, agriculture needs to reduce emissions and/or increase carbon storage. This is a particular challenge in intensive cropping systems. Agricultural soils can act as a sink for carbon storage, and stored carbon can be increased by growing trees, changing cultivation and other cropping practices.

There has also been considerable interest in the use of transgenic crops for biofuel production to provide greener energy, thus providing a renewable fuel with related greenhouse gas savings. Current transgenic events probably do not have sufficient advantage over conventional varieties to overcome the generally poor financial balance of growing crops for biofuels (Ceddia *et al.*, 2009; Ninni, 2009). Edgerton (2009) has however suggested that the development of transgenic crops modified for drought tolerance will provide increased yields in drier areas and increased average yields in rain-fed systems by reducing the effects of sporadic drought and by decreasing water requirements in irrigated systems. This development could help biomass from non-food crops grown on marginal land to be viable as biofuel feedstock.

In summary, there is increasing evidence that suggests that the use of transgenic technology has had direct and indirect benefits in relation to GHGs. Brookes and Barfoot (2009) estimate that between 1996 and 2007, the use of transgenic crops reduced carbon dioxide emissions by 7090 million kg. They estimated that this was equivalent to taking 3.6 million cars off the roads for 1 year. Further, medium-term varietal developments and the wider adoption of conservation tillage in combination with transgenic crops suggest they do have the potential to help meet the targets set as part of the Kyoto protocols.

Water

The MDGs aim to halve the number of people without access to safe drinking water, halve the proportion of people without access to basic sanitation and develop integrated water resource management and efficiency plans by 2015. The International Code of Conduct on the Distribution and Use of Pesticides (FAO, 2005) aims to form voluntary standards for public and private use of pesticides. This code aims to ensure efficient use of pesticides and the establishment of national regulations on pesticide use and where possible to minimise risk to both human health, biodiversity and to reduce the risk of water pollution.

This is an important issue for farmers in Asia, North and Central America and Europe, and agriculture accounts for 86%, 49% and 38% of total annual water withdrawal, respectively. Agricultural practices have a considerable impact on water quality as both fertilisers and pesticides may pollute water courses, thus reduction in pesticide use is likely to improve water quality. Industry data suggests that between 1996 and 2007, there has been an accumulated saving in pesticide of 359 000 metric tons of active ingredient, which equates to a 17.2% reduction in associated environmental impact, in part because of the lower toxicity rating of glyphosate, the key herbicide used for transgenic crops modified for HT (James, 2008).

Many of the herbicides used in conventional crop production systems in the USA have led to their detection in streams, rivers and reservoirs at levels exceeding the maximum contaminant level or health advisory level for drinking water (Thurman *et al.*, 1992). With the commercial introduction of transgenic HT crops in the USA in the late 1990s, it was possible to replace some of the persistent residual herbicide with short half-life contact herbicides that may be more environmentally benign (Fernandez-Cornejo and Caswell, 2006). A recent 4-year study conducted by Shipitalo *et al.* (2008) would support this hypothesis. It showed that the use of transgenic soya bean and maize crops modified to be tolerant to either glyphosate or glufosinate and completely or partially replacing the residual herbicides normally used in conventional crop production systems reduced the environmental impact of herbicide use.

Work reported from Australia (Crossan and Kennedy, 2004) has also shown that the introduction of HT crops can greatly reduce the probability of surface run-off and reduce the risk of water contamination when compared with herbicides used with conventional crops. They reported that the precautionary guideline value for diuron would be exceeded eight times out of ten, whereas a cotton farmer is 500 times more likely to win the lottery (probability one in 10 million) than exceed the precautionary guideline value for glyphosate (probability 1 in five billion 1.9×10^{-10}).

In summary, there is a body of field evidence to indicate that the use of HT crops can significantly reduce surface run-off of herbicides when compared with herbicides used in conventional crops and that this can reduce the need and costs associated with the treatment of drinking water.

Coexistence

Adventitious presence (the accidental or unintentional inclusion of foreign matter) can be problematic and may occasionally lead to economic consequences. There are specific issues relating to coexistence and the possibility that a transgenic crop may have a negative impact on the purity of surrounding crops (Brookes and Barfoot, 2003). Serious concerns related to coexistence have been persistently voiced by some member states of the European Community (EU, 2003). These are generally issues within the productive agro-ecosystem rather than having larger-scale ecological impacts.

Kershen and McHughen (2006) included discussion of coexistence in a review of economic concerns arising from adventitious presence of foreign matter in an agricultural commodity consignment. With regard to approved transgenic crops, the main issues were not food safety or environmental protection but contract specifications and consumer preferences. Langhof *et al.* (2008) noted that although maize has no wild relative in Europe, the introduction of transgenic maize has created the need for rules to keep its adventitious presence in conventional or organic maize below an acceptable level. As in the case of certified seed production, separation by distance is the most common safeguard. Langhof *et al.* conducted field trials and found as expected that outcrossing rates decreased with increasing separation distance, confirming the finding of Messeguer *et al.* (2006) that about 20 m is sufficient to maintain the adventitious presence as a result of pollen flow below the EU tolerance threshold of 0.9%. Rong *et al.* (2007) reported similar tests of separation distances for transgenic and non-transgenic rice, noting that although rice pollen is capable of dispersing at least 100 m from its source, extremely low frequencies of transgene flow occurred, with <0.01% in all cases at a separation distance of 6.2 m.

Messean *et al.* (2006) provide a comprehensive review of coexistence of transgenic and non-transgenic crops in European agriculture, with case studies of seed and crop production of maize, sugar beet and cotton (maize being the only major transgenic crop authorized for cultivation in the EU). Simulations suggested that after the introduction of transgenic rape in a region, adventitious presence will not increase significantly after the second rotation, unless farm-saved seed is used, which would lead to continuous subsequent increase in adventitious presence. For maize, simulations suggested that coexistence in seed production is feasible for a threshold of 0.5% with little or no change in current practice; coexistence of non-transgenic seed with transgenic maize crops would require the isolation distance to be increased from the current 200–300 m to 400–600 m.

Beckie and Hall (2008) reviewed a number of methods for predicting pollen-mediated gene flow in the context of EU concerns surrounding coexistence of transgenic with conventional crops. They concluded that seed growers should be able to achieve adventitious presence well below 0.3% using simple, inexpensive and reliable assays, based on North American experience. Contribution to adventitious presence by oilseed rape volunteers is best mitigated by careful management, including not growing conventional rape on fields previously planted with transgenic cultivars; with rape, gene flow via seeds, not pollen, may be a greater source of adventitious presence. Beckie and Hall found that experimental results and modelling predictions for outcrossing in rape, maize and wheat reveal that an extended isolation barrier is only required between fields of less than about 5 ha to maintain gene flow below the EU threshold; and even for these small fields, a 50 -m barrier is sufficient. This is contrary to most recommendations, which Beckie and Hall believe to be excessively cautious.

Davison (2010) highlighted inconsistency among member states of the EU in the formulation of coexistence regulations on buffer zones and isolation distances, in spite of the creation of the European Coexistence Bureau established jointly by DG Agriculture and EC Joint Research Centre 's Institute for Prospective Technological Studies. Devos *et al.* (2008) noted that it was the European policy of subsidiarity that allowed member states to stipulate distances ranging between 15 and 800 m ostensibly to ensure <0.9% of transgenic maize in conventional maize, commenting on the irony that by introducing coexistence regulations, the EU created a further barrier to the cultivation of transgenic crops. In a subsequent review, (Devos *et al.*, 2009) explored whether national or regional strategies comply with the stated principle that measures should be both science-based and proportionate, concluding that some of the proposed isolation distances are excessive from a scientific basis, out of proportion to heterogeneity in the agricultural landscape and enforce an unreasonable economic disadvantage to farmers by limiting their choice of crop.

Biodiversity

The United Nations Convention on Biological Diversity (CBD; http://www.cbd.int) established at the Earth Summit in Rio de Janeiro in 1992 has three objectives, 'the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources'.

Under the CBD treaty, nations are expected to identify the important components of biological diversity that require conservation, to prevent the introduction of, or to eradicate alien species and to control any risks posed by genetically modified organisms. In relation to targets set under the CBD, it is unlikely that transgenic crops will have a direct measurable positive or adverse effect at a regional scale. However, if the indirect impact of growing transgenic crops is to reduce the ongoing expansion of agricultural zones into non-cultivated ecosystems, then the growing of transgenic crops may help to facilitate the achievement of the wider biodiversity targets.

The implications of transgenic crop introduction for biodiversity are complex and have been the subject of considerable research and debate. (Roy *et al.*, 2003; Velkov *et al.*, 2005; Ferry and Gatehouse, 2009). There is a school of thought that questions whether sufficient biodiversity can be preserved when any farming is carried out on a large scale; Altieri (2004) claimed that there is a form of agrobiodiversity by which traditional methods are used, yields remain stable and food security is adequately protected, but Altieri does not suggest how this could alleviate hunger in developing countries or indeed meet the challenges of rising demand for food.

In the United Kingdom, where the average agricultural system can be described as high output, a 4-year study of the effect that weed management practices associated with transgenic HT crops on wildlife was conducted by UK government agency DEFRA, 1999–2002. A key finding was that biodiversity impacts between transgenic and non-transgenic crops were no greater than the impact of growing different species of conventional crops (ACRE, 2004). A 2-year farm-scale evaluation in Arizona of *Bt* cotton (Cattaneo *et al.*, 2006) reported negative effects on ant diversity and positive effects on beetle diversity, but here again the impacts of the transgenic crop were no greater than those of the non-transgenic crop.

Threats and opportunities facing UK biodiversity were assessed in a wide-ranging foresight exercise (Sutherland *et al.*, 2008); it was noted that a trend towards carbon and water conservation and pollution control will involve changes in conservation management practice, with significant consequences for biodiversity. On this scale of resource management, the minor impacts of transgenic crops on biodiversity are unlikely to be an obstacle to their adoption.

Weed and insect resistance management

The risk that weeds may become resistant to herbicide is well known. A collaborative monitoring study (Heap, 2010) identified 194 herbicide-resistant species in 19 herbicide groups. Of the 194, 19 species show resistance to glycines, including glyphosate. Strategies have accordingly been developed to manage the cultivation of glyphosate-tolerant transgenic crops so as to delay the emergence of resistant weeds. Hurley *et al.* (2009a,b,c) described the weed management programmes, best management practices and the economic effects for growers of transgenic maize, cotton and soya beans. Based on farm surveys in USA, they reported that the emergence of resistant weeds reduced the economic benefit of growing these herbicide-tolerant crops by up to about one-third. The adoption of HT soya beans and no-tillage agriculture in Argentina has increased the use of glyphosate as the main tool to control weeds. This has helped to reduce the density of many weed species but has increased the density of some others that were previously not always part of the community (Qaim and Traxler, 2005). Overall, two weed management practices were considered effective: the use of a residual herbicide with glyphosate and the rotation of crops.

Field studies of soya bean crops in northern and southern regions of USA reported by Scursoni *et al.* (2006) indicate that limited use of glyphosate has little long-term effect on weed diversity. Some of the new weed species found in the fields sprayed with glyphosate on no-till crops have shown a higher tolerance to glyphosate; in Missouri and farther south, long growing seasons allow weeds that emerge and grow late to escape single glyphosate treatments, and this may reduce crop yields substantially if not treated. In contrast, in Iowa and farther north, a single glyphosate application inhibits weeds sufficiently to maintain high soya bean yields obtained from transgenic crops modified to be resistant to glyphosate, but still permits expression of highly effective species richness. Thus, in northern temperate agro-ecosystems, one-pass glyphosate management systems in HT crops may serve agronomic and environmental needs simultaneously. The timing of pesticide application may have a bigger impact on biodiversity than the direct influence of the transgenic crop *per se*. For instance in North America, Bertram and Pedersen (2004) found that the impact on the weed community is mainly because of the changes in the management system (i.e. rotations, tillage systems and herbicides strategies) than the transgenic trait *per se*.

May *et al.* (2005) found that the use of HT sugar beet provided greater flexibility to manipulate weed populations. They found that without yield loss, the transgenic options enhanced weed seed banks and autumn bird food availability compared with conventional management and provided early season benefits to invertebrates and nesting birds.

The US Environmental Protection Agency has published a risk assessment procedure focused on plants expressing insecticidal proteins available in the commercial market, evaluated for potential non-target invertebrate risks (US

EPA, 2007). This relates to concerns that the use of broad-spectrum herbicides such as glyphosate could reduce weed seed availability and thus predation by a range of insects and also fears that IR varieties would have a negative impact on non-target species. Initial assessments are laboratory based using surrogate non-target organisms; if potential toxicity is identified, field experiments are then undertaken. Duan *et al.* (2009) used meta-analyses to test whether laboratory studies are consistent with field studies and reported findings that supported the validity of EPA's tiered approach, provided that the laboratory studies exposed non-target organisms to a full variety of ecological contexts, including indirect exposure via an intervening trophic level.

Monsanto maintain a website for insect-resistant MON810 YieldGard^{TM} maize (Monsanto, 2010). The website includes guidance for adopters on insect resistance management, and EU requirements for compliance. The advice for the *correct* use of MON810 maize is that the adopter must plant a refuge maintained and managed in the same way as the crop: it must be planted at the same time, irrigated in the same way and receive the same inputs. At least 20% of the hectares must be planted with maize hybrids that do not contain *Bt* technology, and the refuge area can be treated with insecticides only when corn borer pressure exceeds economic thresholds. Monsanto initiated a surveillance monitoring programme based on farm surveys (Monsanto, 2008), from which it was found that 18% of farmers planting MON810 in Spain in 2008 did not plant a refuge, an improvement on the 26% who did not plant refuges in 2007. In spite of these levels of non-compliance, monitoring did not reveal any resistance in insect populations.

Bt maize has been grown at the Vaalharts irrigation scheme in the Republic of South Africa since 1998, but Kruger *et al.* (2009) reported that refuge compliance was initially low, and farmers who did provide refuges generally preferred a permitted refuge option where 5% of the main crop area is planted to conventional maize. This practice seems to have allowed exposure of migrating larvae to sub-lethal doses of *Bt* toxin. Stem borer damage to *Bt* maize was first observed during 2005/2006, and during 2007/2008, stem borer infestation required the use of sprayed insecticides. Kruger *et al.* commented that farmers had become over-confident in *Bt* technology and ceased to monitor the crop for infestation; Kruger *et al.* concluded that non-compliance with refuge requirements contributed to selection pressure leading to insect tolerance to the toxin.

Sanvido *et al.* (2007) reviewed the environmental effects of 10 years of commercial cultivation of transgenic crops, including the loss of natural habitats caused by conversion of natural ecosystems into agricultural land, seen in relation to the environmental impacts of modern agriculture that has been practised over many decades. They opened their review by observing that the approval of transgenic crop varieties is more rigorously regulated than that of conventionally bred crops. They reached the firm conclusion that data available up to 2009 provided no scientific evidence that the commercial cultivation of transgenic crops has caused any impacts beyond those caused by conventional agricultural management practices. They noted that a truly precautionary policy towards approval of transgenic varieties should compare the risk of adoption against the risk of non-adoption.

In relation to insecticides, the more targeted application of the insecticidal chemical (plant expression as opposed to spray application) may limit the exposure level of many field arthropods. Beneficial, non-target arthropods can become exposed to insecticidal proteins produced in transgenic plants in several ways: by feeding on the plant parts themselves or through feeding on target or non-target herbivorous insects. Pilcher *et al.* (2005) studied the effect of *Bt* maize on non-target arthropods and found no significant effect on abundance of generalist predators. Mulligan *et al.* (2006) studied the potential impact of insect-resistant oilseed rape on an ecologically important beneficial predator, compared with the potential impact of the most widely used UK pesticide in rape cultivation. Neither genetic modification nor conventional pesticide treatment negatively affected the life history parameters of the beneficial insect. The result suggests that the cultivation of insect-resistant transgenic crops will have no greater impact than present cultivation methods.

Lu *et al.* (2010) conducted field trials over 10 years in a region of China where *Bt* cotton is widely grown and where the associated reduction in pesticide spraying has allowed unrestrained build-up of the population of mired bugs, which damaged not only the cotton crop but also adjacent fruit crops. Lu *et al.* concluded that comprehensive risk management is necessary to ensure sustainability of transgenic technologies. Lövei *et al.* (2009) reviewed numerous reports of the impact of *Bt* crops in laboratory settings and recommended widening the scope of environmental risk assessment. Shelton *et al.* (2009) agreed the importance of risk assessment of transgenic insect-resistant crops but were critical of the statistical methods employed by Lovei *et al.*

In summary, Baucom and Holt (2009) identified a need for collaboration between applied weed scientists and evolutionary ecologists, observing that weed adaptation to agricultural systems provides a view into the process of evolution as well as a challenge to food supply, particularly the processes involved in the evolution of herbicide resistance. An alliance of practical weed science with hypothesis-driven ecology may lead to better understanding not only of mutations that give weed persistence but also the genetic involvement in constraint of weed populations.

Social dimension

The social dimension is of paramount importance in the MDGs, particular relating to health, education, poverty reduction and human disease control. While early transgenic events were not engineered to have a direct impact on these factors, their take-up and use has had indirect effects in many areas, and new events and those in the pipeline may aid disease prevention and lead to health benefits (Newell-McGloughlin, 2008; Stein and Rodriguez-Cerezo, 2009). Earlier sections in this paper discussed the potential for transgenic crops to increase incomes and thus to alleviate poverty. Literature suggests that as incomes rise, people are able to access better education and health care, which thus impacts on the social dimension of sustainability (and indeed this principle underlies the MDGs). In the following sections, we consider indirect and direct human health effects of growing of transgenic crops.

Indirect health impacts

Indirect health effects will mainly arise from changes in the frequency of use and reductions in pesticide toxicity. In relation to toxicity, the Environmental Impact Quotient (EIQ) is a useful measure as it considers risks to farm workers and consumers as well as ecological risks (Brimner *et al.*, 2005). Pesticides with high EIQ values are considered to have a higher risk of potential impacts than those with low EIQs. Multiplied by the amount of pesticide applied, the EIQ can be used to calculate the potential environmental impact (EI) of individual pesticides or pest management programmes involving several active ingredients.

In Australia, with reference to *Bt* cotton, Knox *et al.* (2006) considered the impact of the transgenic proteins Cry1Ac and Cry2Ab on EIQ values. While the average insecticide EI for conventional cotton was 135 kg a.i./ha, the value for the *Bt* variety with two inserted genes was only 28 kg a.i./ha. Results of the EI evaluation indicate that there was a net reduction of at least 64% in EI from growing *Bt* cotton compared with conventional non-transgenic cotton.

In Canada, the growth of HT canola varieties increased from 10% in 1996, when the technology was first introduced, to 80% of the total area in 2000. From 1995 to 2000, the amount of herbicide-active ingredient applied/ha of canola declined by 43% and the EI per ha declined by 37%. Since 1996, herbicide use has shifted from broadcast applications of soil-active herbicides to post-emergence applications of herbicides with broad-spectrum foliar activity. The decline in herbicide use and EI since the introduction of HT varieties was because of increased use of chemicals with lower application rates, a reduced number of applications and a decreased need for herbicide combinations (Brimner *et al.*, 2004).

It is also worth noting that the introduction of HT soya beans, in particular, has changed patterns of use of chemical herbicides with glyphosate now being the most dominant herbicide, accounting for 92% of herbicide use on soya bean. It is classified internationally as a toxicity class IV pesticide, less toxic than many of the previously utilized herbicides.

Workers can be exposed to pesticides through direct skin contact or inhalation during application. Such exposure also may occur when safety periods between application and harvest are ignored or when pesticides are overused or used improperly. Pesticides from aerial spraying may also drift into neighbouring areas and expose residents. Research has indicated reduced incidence of pesticide poisonings in South Africa since the introduction of transgenic crops (Bennett *et al.*, 2006) and that reduced pesticide use has had health benefits among Chinese farmers (Huang *et al.*, 2002).

Direct health impacts

To date, direct health benefits have been relatively limited, although transgenic events in the pipeline could potentially have considerable health benefits. *Bt* varieties of maize were produced to protect plants against the European Corn Borer, which if pest levels are high can reduce crop yield by about 10%. There is a direct relationship between European Corn Borer infestation and ear rot, which is a result of secondary fungal plant infections of *Fusarium*, which results in greatly elevated levels of mycotoxins often in the form of fumonisin. The accumulation of mycotoxins in food and feed represents a major threat to human health and is linked to oesophageal cancer and neural tube defects. Major economic losses are associated with the effect of mycotoxins on human health and animal productivity. In the USA, Munkvold *et al.* (1999) showed that the fumonisin content of maize grain produced from *Bt* varieties was greatly reduced when compared with grain from conventional varieties. The conclusion is that the use of *Bt* maize not only has the potential to increase grain yield in areas where there is high infestation of European Corn Borer but will provide safer food and feed for humans and animals.

Work is also well advanced in the development of transgenic crops that will have a direct impact on health. For example, Chu *et al.* (2008) has shown that the most potent peanut allergens can be silenced in transgenic plants. Newell-McGloughlin (2008) lists examples of developments that improve protein quality, modify carbohydrates and fatty acids, add micronutrients and introduce functional secondary metabolites.

Nutrition

There are well-known dietary benefits associated with very long-chain omega-3 polyunsaturated fatty acids, originally identified with fish oils. Oilseed plants rich in omega-3 fatty acids, such as flax and walnut oils, contain only the 18-carbon omega-3 polyunsaturated fatty acid alpha-linolenic acid, which is poorly converted by the human body, but Damude and Kinney (2008) showed that is now possible to use genetic engineering to produce oilseeds such as soybean and canola that have nutritional properties similar to fish oils. Studies have shown that the use of oil from transgenic soya in which the fatty acid metabolic pathways have been modified can increase the n-3 VLC-PUFAs of chicken meat (Rymer and Givens, 2009).

Mayer *et al.* (2008) note that the desired traits for biofortification may not be present at all in a food crop; the best-known example being Golden Rice, in which the carotenoid biosynthetic pathway has been reconstituted in non-carotenogenic endosperm tissue, as a means to deliver provitamin A. The inability of governments worldwide to agree to distribute Golden Rice stirs strong emotions and little progress in terms of growth has been made despite the properties of Golden Rice being well known. (Golden Rice Project 2000).

Stevens and Winter-Nelson (2008) examined the acceptance of provitamin A-biofortified maize through taste tests and a trading experiment conducted in Maputo, Mozambique. These results indicate that orange maize meal is an acceptable product to many consumers. Such potential developments are of huge potential significance as Black *et al.* (2008) estimate that 600 000 children die each year from vitamin A deficiency. Clearly, these aspects relating to health and nutrition are a fundamental part of the MDGs.

Nutrition has already been enhanced via biotechnology with quality protein maize (QPM), developed specifically to improve amino acid composition with the aim of reducing malnutrition in parts of Sub-Saharan Africa. Krivanek *et al.* (2007) report that the International Maize and Wheat Improvement Centre (CIMMYT) has collaborated with IITA in Ibadan, Nigeria, and National Agricultural Research Systems (NARS) to develop a broad range of QPM cultivars. Breeding and dissemination is making good progress, with commercial cultivars released in 17 countries.

In conclusion, it appears that in relation to the social dimension of sustainable development, transgenic crops can have indirect impacts on health particularly via reduction in the handling and use of pesticide. However, ongoing developments in biotechnology, particularly related to the nutritional modification and enhancement of food, have the potential to radically improve human health and nutrition in both developing and developed countries.

Discussion and conclusions

It is acknowledged that the world will face a number of serious challenges if development is to proceed on a sustainable pathway. Indeed, many people in the world still live in extreme poverty and are without adequate nutrition, health and education. World population continues to grow at 80 M per annum, and it has been estimated that the requirement for food will double by 2050. However, there is little or no scope to expand the existing agricultural footprint without further damaging natural ecosystems. Climate change threatens to reduce productivity in many regions and is itself driven by the use of fossil fuels that provide a great deal of the motive power in intensive and productive agricultural systems.

To meet these challenges humankind is likely to require a range of productive options and tools if wider-scale social deprivation and environmental degradation is to be avoided. Crop biotechnologies appear to provide such a range of tools and have started, and may continue, to contribute to sustainable development. In this paper, we have reviewed a wide range of literature that suggests transgenic crops can contribute to international targets and goals related to sustainable development. For instance, China has invested very extensively in biotechnology with the aim of ensuring food security. For example, work is well advanced with rice varieties that are tolerant of drought and other stresses (Huang *et al.*, 2009).

However, the growing of transgenic crops continues to be controversial despite the 134 Mha grown in 25 countries, the cumulative area grown since 1996 being over 2 BN ha. Fears and claims of possible adverse effects of biotech foods and crops on humans and the environment have yet to be substantiated; no ill effects have been documented after 12 years of extensive cultivation in diverse environments, and after the consumption of biotech foods by more than a billion humans and by a larger number of animals. Lemaux (2008) offers an extensive review of ways in which research using rDNA methods has 'opened the door' to changing agricultural crops in ways not previously possible. Although she recognizes the need to proceed with caution, Lemaux sees a responsibility to utilize the technology where it can improve human health, preserve the environment and assist in providing adequate nutrition.

Looking further into the future, Ridgwell *et al.* (2009) note that crop plants exert an important influence over the climatic energy budget, because of differences in their albedo (solar reflectivity) compared to soils and natural vegetation. They propose a bio-geoengineering approach to mitigate surface warming, in which crop varieties having specific leaf glossiness and canopy morphological traits are specifically chosen to maximize solar reflectivity. They estimate the near-term potential for bio-geoengineering to be a summertime cooling of more than 1 °C throughout much of central North America and mid-latitude Eurasia, equivalent to seasonally offsetting approximately one-fifth of regional warming because of doubling of atmospheric CO_2.

The review undertaken here suggests there have been potential benefits since the release of transgenic crops and that these can be evidenced in each of the three key dimensions of sustainable development.

Economic dimension

Poverty alleviation is a cornerstone of sustainable development and is critical to progress the MDGs. Most of the evidence suggests that at worst, transgenic crops are cost neutral, although the bulk of evidence suggests an economic benefit across the range of countries growing them. Analysis by Brookes and Barfoot (2008) suggests that the cost of accessing transgenic technology worldwide in 2006 was US$2687M, leaving farmers worldwide with net benefit of US$6915M. Of these totals, they estimate that farmers in developing countries pay only US$742M for the technology and achieve benefits of US$3713M, a cost/benefit ratio of 5 to 1. Advantages relate to input savings and in some cases increases in crop yield and quality.

Some researchers have attempted to quantify the longer-term economic consequences of adopting transgenic crops. The work by Wesseler *et al.* (2007) on take-up in the then EU-15 suggested that there were good economic reasons for adopting *Bt* and HT maize immediately when evaluating at the national economy or farm level. They went on to suggest that the early adoption by Spain of *Bt* maize led to an economic advantage of €135M, while the decision of France not to adopt over the same 5 -year period meant a lost economic opportunity of about €310M.

Environmental dimension

Soil erosion, desertification, climate change, water related issues and biodiversity are all of international importance in relation to sustainable development, and evidence suggests that transgenic crops can have positive impacts in many of these areas.

For instance, transgenic crops have the potential to reduce soil erosion via association with lower levels of cultivation. Currently available transgenic events are all related to the modification of pesticide use, and this has the potential to reduce the environmental loading and in particular the movement of highly toxic pesticides into water. When combined with reductions in field operations associated with multiple pass spraying, this can lead to reductions in the amount of GHGs emitted. In these key areas, transgenic crops are already having benefits, and it is likely that these will continue to accumulate as the areas being grown expand.

Biodiversity impacts related to transgenic crops are not as easy to quantify. Losey *et al.* (1999) caused alarm with results of a test in which pollen from *Bt* maize was fed to monarch butterfly caterpillars, from which the caterpillars died; several independent investigations subsequently showed the risk of harm to those butterflies in the field to be vanishingly small (Conner *et al.*, 2003). The farm-scale evaluation in the United Kingdom illustrated some biodiversity benefits related to HT maize but some negative impacts for other crops (i.e. spring or winter oilseed rape and sugar beet). Overall, it seems that in many cases, it is the type and management of the overall agricultural system that has an overriding impact on biodiversity, rather than the transgenic nature (or not) of the seed planted.

Social dimension

The MDGs are a clear driving force in relation to sustainable development. Transgenic crops are having health benefits at the simplest level as farmers are using and handling less highly toxic pesticide. The evidence related to increased income in developing countries also shows that this leads to increased benefits in relation to nutrition, health and education, all key development goals. In addition, events in the pipeline suggest much more tangible benefits related to nutritionally enhanced foods, for instance Golden Rice.

In conclusion, although many individuals and organizations continue to question the need for, and the benefits of transgenic crops, the challenges facing farmers in relation to feeding an ever increasing world population from a diminishing resource base continue and indeed are growing. Transgenic crops certainly do not provide a 'silver bullet' in relation to sustainable development, but the research evidence presented here suggests that they provide a suite of tools that need to be and should remain available to food producers. The recent 'Agriculture at a Crossroads' (IAASTD, 2009) also appears to advocate multifunctional systems with a range of technologies and systems being used to by agriculturalists. Many scientists believe new transgenic events in the medium term could provide further benefits. Those events in the pipeline through to 2015 mainly expand the *Bt* and HT options across a wider range of species and will be related to the stacking of traits. Stein and Rodriguez-Cerezo (2009) predict a total of 124 events by 2015 with 15 new rice events and eight related to potatoes.

Beyond 2015, it is difficult to predict what will come to market and when, or indeed what the nature and extent of international and national regulatory frameworks relating to transgenic crops will be. However, it is likely that new crop events related to nutritional benefits, nitrogen use efficiency, drought and salt tolerance and yield enhancement will be available by 2020 by which time the world population is predicted to be about 8 BN, 1.3 BN more than today. International agreement to responsibly deploy all safe tools, including transgenic crops at our disposal to minimize environmental impact while maximizing output, would have a major global impact in relation to sustainable development.

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