When bad science makes good headlines: *Bt* maize and regulatory bans

To the Editor:

The safety of transgenic crops and derived foods continues to be a contentious issue of public and political debate. The debate is confounded when poorly designed studies that report unusual and controversial results receive a disproportionate amount of attention in the scientific and lay press, which in turn, influences both public policy and perceptions about agbiotech. This is illustrated by the selective reporting of scientific literature in some European countries to support moratoria on the cultivation of MON810, a transgenic maize expressing the Cry1Ab insecticidal protein isolated from *Bacillus thuringiensis* (*Bt*). Countries, such as France and Germany, have put these moratoria in place, even though the GMO Panel of the European Food Safety Authority has concluded that MON810 is unlikely to have any adverse effect on the environment in the context of its intended uses[1].

A common concern among regulatory authorities is the potential for a transgenic plant to have adverse impacts on nontarget arthropods (NTAs) that are valued for the ecosystem services they provide (e.g., biological control of pest organisms, pollination and decomposition) or for aesthetic or other anthropocentric reasons[2,3]. This risk is particularly evident for transgenic plants that express insecticidal proteins to control specific pests. The most studied transgenic plants with respect to NTA effects are insect-protected maize events that express Cry1Ab to control lepidopteran pests. Such *Bt* maize hybrids have been grown on millions of hectares since 1996.

Numerous laboratory toxicity studies and field experiments, as well as years of field observations in countries where *Bt* maize is cultivated, have provided evidence that the Cry1Ab protein expressed in *Bt* maize does not cause adverse effects on arthropods outside the order Lepidoptera (butterflies and moths), the group that contains the target pests. Supporting data have been analyzed in reviews and meta-analyses[4–8].

Despite this preponderance of evidence, a few outlier studies claiming adverse effects of Cry1Ab to nonlepidopteran species have been the subject of persistent media coverage and often undue consideration by regulators. The potential of such studies to inform the risk assessment of *Bt* crops depends on whether the effects observed allow the novel conclusion of Cry protein toxicity, or whether they are caused by other confounding factors associated with the design of the study, and thus provide no confirming evidence of toxicity. This requires a careful evaluation of the underlying test protocol.

Laboratory studies intended to assess the impact of purified or plant-expressed insecticidal proteins on nontarget arthropods must follow basic test criteria to produce quality data that can be reliably interpreted[9]. Primary criteria include thorough description and characterization of the test material (including the stability and bioactivity of the test protein), quantification of the test substance concentration and confirmation of the exposure by the test organism to the protein, and inclusion of appropriate control treatments. These key criteria and others allow assessment of the suitability of the test systems, the test organisms and the test conditions that are required to clearly link observed effects to the test compound.

We have analyzed the available NTA studies conducted with purified Cry1Ab protein or tissue from *Bt* maize plants (bi-trophic exposure) published in peer-reviewed journals to date in accordance with these study quality criteria (**Supplementary Notes**). This includes a total of 55 laboratory studies presented in 36 peer-reviewed publications with 32 NTA species. From these, four publications dealing with the aquatic organisms *Daphnia magna*[10] and Trichoptera larvae[11], and larvae of the two predators *Adalia bipunctata*[12] and *Chrysoperla carnea*[13] have reported putative toxic effects of Cry1Ab. The first three studies, together with unpublished information on adverse effects of *Bt* maize on saprophagous Diptera, were cited as new evidence by the German government when invoking a safeguard clause in European genetic technology legislation[14] to suspend the approval of MON810-derived varieties in April 2009 because of the belief that MON810 posed a hazard to the environment[15]. None of these studies, however, provides reliable evidence regarding non-Lepidoptera activity of Cry1Ab at the concentrations expressed in *Bt* maize, and none of the results have been corroborated by other research groups in prior or later experiments (**Supplementary Notes**). Despite the nonconclusive nature of these studies, the ban of MON810 in Germany is still in force.

This example demonstrates that NTA studies that report false-positive effects of Cry

Table 1 Questions to assess the value to regulatory risk assessment of a study on *Bt* crops with unprecedented results

Question	Background	Example
Does the study evaluate an environmental risk that is relevant to the receiving environment?	The initial step in any risk assessment (also known as problem formulation) directs the scope of the assessment and defines the environmental entities that are to be protected. This includes a statement of clear protection goals, which are the objectives of environmental policies typically defined in law or regulations. Protection goals may vary among different jurisdictions.	A common protection goal is protection of nontarget organisms that are valued for the ecosystem services they provide or for aesthetic or other anthropocentric reasons.
Does the study indicate a novel hazard (unexpected adverse effect) that has not previously been addressed?	Sometimes hazards reported in the literature have already been taken into consideration in premarket risk assessments conducted for approved transgenic crops.	A new study reports effects of Cry1Ab on larvae of a nontarget butterfly species that is similar in magnitude to that reported for other species. This report should be of no particular relevance because Cry1Ab toxicity to Lepidoptera is well established.
Is the study properly designed and conducted, and are conclusions supported by the data?	Every study needs to address a well-formulated hypothesis and be designed in a way that this hypothesis is critically and accurately tested. Study design is an important factor to prevent false negatives and false positives. Data, methods, underlying assumptions and limitations should be clearly documented. Interpretation of the data should be related to the hypothesis and not be speculative. If the results are counter to a large body of prior work indicating no effect, then the study methods, underlying assumptions and limitations should be thoroughly assessed.	Studies with unusually high control mortality levels are indicative of problems with overall study design and execution, for example, unhealthy test arthropods.

proteins have consequences that go beyond triggering additional testing. Such studies can have a profound impact on product-specific decision making, affect policy direction and technical guidance, lead to bans or delays in decision making[16] and distort research priorities for public-sector funding[17].

The careful evaluation of test protocols is a critical step that is sometimes missed by regulatory risk assessors or, more commonly, others who parse the scientific literature looking for studies that can be interpreted as evidence for the adverse environmental impact of transgenic plants, such as occurred in Germany. Risk assessors should consider the quality of evidence when evaluating individual scientific publications, particularly when a study's conclusion challenges an accepted body of knowledge. This has been explicitly recognized by the Australian Office of the Gene Technology Regulator[18] but rarely by other biotech regulatory authorities.

The relevance of published conclusions about hazards to NTAs that have been attributed to transgenic plants previously assessed as safe need to be carefully evaluated by, for example, answering the questions we have collected in **Table 1**. In doing so, regulatory authorities can put new scientific data into context and compare their significance relative to conclusions from prior environmental risk assessments. Only in cases where all three questions are answered with 'yes', should the study trigger reassessment of the conclusions from the original environmental risk assessment and then a decision as to whether additional investigation and/or other regulatory action is warranted. Such a logical, step-wise assessment of new scientific findings requires expertise in risk assessment and a thorough understanding of the available scientific evidence and information. This assessment process clarifies the need to explicitly consider the quality and relevance of new findings, and helps to justify the rejection of certain studies that do not meet defined quality criteria.

Environmental risk assessment of transgenic crops should be a scientifically defensible approach to ensuring that environmental protection goals are appropriately considered before a transgenic crop is released for cultivation. However, the regulation of transgenic crops continues to be highly politicized and so it is essential that regulatory authorities, or the scientists that evaluate data on their behalf, be discriminating about the legitimacy of the studies that they consider during the evaluation process, irrespective of their source. This evaluation should include both the quality of the study itself as well as its relevance to the risk assessment process as described in regulations and associated guidance. The consequences of a poorly informed decision can be substantial, resulting in the deployment of transgenic plants that may be harmful to the receiving environment. More likely, ill-informed decisions lead to the rejection of potentially useful transgenic plants, impeding access to environmental and/or financial benefits by farmers, product developers and other participants in the agricultural production and value chains.

A recent example of this phenomenon arose with the publication by Seralini *et al.*[19] of a study purporting to show increased pathological effects such as tumors in rats fed transgenic maize event NK603, with and without glyphosate, in a two-year feeding study. Doubts were cast on the conclusions of the study by regulators from the European Food Safety Authority, six European Union Member States, Food Standards Australia New Zealand and Health Canada, each of which identified serious deficiencies in the design and methodology of the study[20–22]. Nevertheless, the paper has received extensive coverage in the lay and scientific media and was attributed by the governments of Russia and Kenya in their decisions to ban the import of NK603 and transgenic foods, respectively. The longer term impact of Seralini *et al.*[19] on regulatory risk assessment and decision making is presently unknown, but the paper has heightened the debate about the quality of evidence and the role of the media in communicating unexpected transgenic crop effects[23,24].

The illegitimate use of science to further political agendas (or capture media attention), both within and outside of government, is certainly not unique to agbiotech. However, there seems to be a disproportionate amount of attention paid in both the scientific and lay press to studies that dispute the preponderance of evidence about the environmental safety of certain transgenic crops, irrespective of the quality of the study itself and its relevance to transgenic crop regulation. This perpetuates unfounded concerns about approved GE crops, leads to overly precautious and expensive regulations, and limits opportunities to access and apply genetic engineering to address pressing food security, social, economic and environmental challenges.

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The authors declare no competing financial interests.

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