Opinion

Is biotechnology a victim of anti-science bias in scientific journals?

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Primarily outside the scientific community, misapprehensions and misinformation about recombinant DNA-modified (also known as 'genetically modified', or 'GM') plants have generated significant 'pseudo-controversy' over their safety that has resulted in unscientific and excessive regulation (with attendant inflated development costs) and disappointing progress. But pseudo-controversy and sensational claims have originated within the scientific community as well, and even scholarly journals' treatment of the subject has been at times unscientific, one-sided and irresponsible. These shortcomings have helped to perpetuate 'The Big Lie' – that recombinant DNA technology applied to agriculture and food production is unproven, unsafe, untested, unregulated and unwanted. Those misconceptions, in turn, have given rise to unwarranted opposition and tortuous, distorted public policy.

Introduction

The production of pharmaceuticals with recombinant DNA technology [also known as gene-splicing or genetic modification] has enjoyed significant successes over a quarter century, with minimal controversy. However, the use of recombinant DNA-modified plants for food, feed and environmental applications has not fared as well. Primarily outside the scientific community, misapprehensions and misinformation have generated significant 'pseudo-controversy' over the plants' safety. The ensuing misconceptions have resulted in excessive, unscientific regulation, inflated development costs and disappointing progress. But pseudo-controversy and sensational, inaccurate claims by activists have appeared within the scientific community as well, and even scholarly journals' treatment of the subject – especially the aspects related to environmental or health risks – has been at times unscientific, one-sided and irresponsible. Examples of the failure of editorial judgment and/or peer review abound, including the appearance of flawed, misleading articles in *Nature*, *The Lancet*, *Science* and *Proceedings of the National Academy of Sciences USA* (*PNAS*) that never should have been published.

Inconsistencies in editorial policies

Often, these shortcomings reflect internal inconsistencies. For example, in 1992 *Nature* editorialized: 'The same physical and biological laws govern the response of organisms modified by modern molecular and cellular methods and those produced by classical methods ... [Therefore] no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques that modify DNA and transfer genes' [1]. These conclusions seem clear and unequivocal (as well as obvious) enough, but more recently *Nature* has rejected or neglected such sentiments in both editorials and the reporting of 'news'. Their news correspondents sometimes seem to be ignorant of context and to rely extensively on unreliable, biased sources; and the supervising editors apparently are unwilling or unable to correct them. Repeatedly, *Nature* has offered undue credibility and coverage to doctrinaire critics and skeptics of recombinant DNA technology. A recent example occurred in a September 2007 news article, 'Biotech crop rules get rewrite' [2]. This description of a U.S. Department of Agriculture (USDA) initiative to revise the regulation of recombinant DNA-modified organisms was exceedingly one-sided and misleading. The article cited the concerns of 'critics' who believe that the changes in regulation 'will not go far enough to protect the environment and public health', whereas an examination of the comments in the official docket (USDA dossier #APHIS-2006-0112) suggests that a fairer and more accurate rendering would be: 'many prominent academic experts fear that the changes will not make the existing flawed regulatory approach more scientifically defensible and risk-based.'

As numerous academics pointed out in their comments in the official docket, the existing USDA regulatory approach – the basic tenet of which is that the use of the most precise and predictable techniques (*viz*, recombinant DNA) elicits a discriminatory and excessive regulatory regime – violates the principle of proportionality (which holds that the degree of regulatory scrutiny should be commensurate with the degree of risk posed by a product or activity); under the USDA's oversight, the amount of scrutiny applied to field trials and commercialization of new plant varieties is actually *inversely* related to risk. Paradoxically, recombinant DNA-modified organisms, the most precisely crafted and most predictable organisms – that is, those generally posing the *least* risk – are the *most* regulated. Excessive regulation has markedly inflated the costs of performing field trials; a field trial with a recombinant DNA-modified plant costs 10–20 times as much as one with a phenotypically identical plant modified with conventional techniques [3].

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The approach to regulation taken by the USDA conflicts not only with scientific consensus and common sense but also with official overarching statements by the U.S. government about the principles that should guide regulatory policy, which are congruent with the viewpoint of the 1992 *Nature* editorial quoted above. In turn, this viewpoint reflects an authoritative 1989 analysis of genetic modification technologies by the United States National Research Council that summarized the contemporary scientific consensus: 'With classical techniques of gene transfer, a variable number of genes can be transferred, the number depending on the mechanism of transfer; but predicting the precise number or the traits that have been transferred is difficult, and we cannot always predict the phenotypic expression that will result. With organisms modified by molecular methods, we are in a better, if not perfect, position to predict the phenotypic expression' [4].

Nature's correspondent in the September 2007 article ignored this essential context completely. We will not speculate whether *Nature*'s slanted characterization of the responses to the USDA's proposal was a rookie correspondent's mistake or whether it represents the insensitivity of the journal's editors to the importance of science as the basis for public policy.

The worst case: publication of flawed research

The publication of shoddy or misleading news articles pales beside the appearance of flawed research articles – for example, the 2001 paper by Quist and Chapela in *Nature* that ostensibly demonstrated gene flow from maize that contains genetic material from *Bacillus thuringiensis* (Bt-maize) into native landraces of maize in Oaxaca, Mexico [5]. These supposedly positive results were based on dubious methodology, as colleagues had pointed out to the authors months before submission to *Nature*. The publication of the article triggered scientific criticism from major research groups that was published subsequently in *Nature* [6,7], and eventually the original article was condemned by the editor in chief: 'In light of these discussions and the diverse advice received, *Nature* has concluded that the evidence available is not sufficient to justify the publication of the original paper' [8]. However, although both reviewers and editors rejected additional evidence submitted subsequently by the original authors to support their original conclusions, *Nature* published the new 'evidence' [9] in order 'to allow our readers to judge the science for themselves' [8]. This seems to be an abdication of the usual formal process of peer review, the purpose of which is to subject experimental data to expert vetting prior to publication. Philip Campbell, the editor of *Nature*, avers that, 'The independence of our editorial decision-making from partisan anti- or pro-technology agendas and from commercial interests is paramount in our role as a journal' [10]. Perhaps he should add 'competence and professional behaviour of editors and reviewers' to what *Nature* considers to be 'paramount'.

It is noteworthy that later examination of 150 000 maize samples in Oaxaca found no trace of Bt genes [11], and no other group has confirmed the results of Quist and Chapela. Ironically, however, even if the original report by Quist and Chapela had been correct, the finding of gene flow would have been inconsequential. As botanist Peter Raven observed, 'Whether or not transgenes are present in landraces in Oaxaca at present, they will inevitably be found in them as time passes, because of the nature of the indigenous agriculture.' He added, 'There they will persist if they confer a selective advantage on the plants in which they occur, or they may disappear if they do not confer such an advantage in the prevailing conditions. Such genes are no more 'invaders' into the populations concerned than any other genes' [12].

Nature is not alone in exhibiting an apparent bias against biotechnology. In 2000, *Science* published a 'research article' by L.L. Wolfenbarger and P.R. Phifer that was both trivial and obviously flawed [13]. Although the authors claimed to have evaluated the 'ecological risks and benefits of genetically engineered plants', they ignored persuasive theoretical and experimental evidence of the safety and utility of these products. Moreover, the authors' focus on 'transgenic' plants – defined arbitrarily as those that contain genes transferred across species lines, but only when this has been accomplished by recombinant DNA techniques – ignored the scientific consensus that genetic modification is a continuum employing many technologies and that recombinant organisms are not a meaningful 'category'. Millions of new genetic variants of plants field tested each year are derived from 'wide crosses': hybridizations in which genes have been moved across species or genus barriers. For example, *Triticum agropyrotriticum,* a man-made 'species' that resulted from combining genes from bread wheat and a grass called quackgrass or couchgrass, possesses all the chromosomes of wheat and one extra whole genome from the quackgrass; a pluot is a plum–apricot hybrid; and triticale is a wheat–rye hybrid. Why were such 'non-molecular transgenic varieties' (as they might be called) – of which there are thousands in commerce – not included in the analysis?

The authors invoke the tautology that 'the complexity of ecological systems presents considerable challenges for experiments to assess the risks and benefits and inevitable uncertainties of genetically engineered plants,' so their lame conclusion about recombinant DNA-modified transgenic plants is hardly surprising: 'collectively, existing studies emphasize that [risks and benefits] can vary spatially, temporally, and according to the trait and cultivar modified.' In other words, exactly what scientists know to be true about plants modified with any genetic technique.

However, at the time of Wolfenbarger's and Pfifer's 'research' there were already compelling examples of the significant benefits (in addition to the obvious greater precision and assurance of predictability) of recombinant DNA-modified organisms, including higher yields, nutritional enhancements, less use of chemical pesticides and more no-till farming with less soil erosion, runoff of chemicals and release of carbon dioxide to the environment [14].

Another egregious and exceedingly harmful example of apparent anti-biotechnology bias was the publication of the paper by Arpad Pusztai in *The Lancet*, which claimed to show that adding a snowdrop plant gene that codes for a protein known to be toxic to certain insects caused damage to the immune system and stimulated abnormal cell division in the digestive tract of laboratory rats [15]. However, many research groups have shown that Pusztai's research methodology was fundamentally flawed and that no conclusions about the safety of biotech foods can be drawn from his data – or, indeed, from such an experimental design. Pusztai fed the rats primarily with raw potatoes (which are toxic when they comprise a significant fraction of the diet) and made no attempt to provide nutritionally balanced diets. As a consequence, *all* the rats in the study experienced adverse health effects. Moreover, Pusztai used an experimental potato variety that lacked several key vitamins. Any effects that he might have observed were likely to be caused by these factors. Finally, trained independent experts could see no differences between the tissue preparations from the control and experimental groups. What sort of peer review process could fail to perceive these deficiencies and to reject this paper?

After an extensive review, the British Royal Society issued a statement that detailed the ways in which the experiment was fatally flawed, concluding: 'On the basis of this paper, it is wrong to conclude that there are human health concerns with the process of [recombinant DNA technology] itself, or even with the particular genes inserted into these [recombinant DNA-modified] potatoes' [16].

The editors of *The Lancet*, in which Pusztai's research appeared, remonstrated that, in spite of the article's admittedly deficient methodology – and over the strenuous objections of the paper's referees – they published it to 'make constructive progress in the debate between scientists, the media, and the general public' about a highly politically charged issue (http://news.bbc.co.uk/2/hi/science/nature/472192.stm, accessed Oct. 19, 2007). Unleashing such a sham has proved to be anything but constructive because its publication in *The Lancet* is frequently cited as presumptive validation of the authors' spurious conclusions – not unlike referring to pre-Copernican literature as proof that the Sun revolves around the Earth. The rationalization by the editors of *The Lancet* is outrageous and irresponsible, and it makes a mockery of the peer review of research papers.

The most recent example of egregious failures of editorial and peer review occurred in a 'research' article published in September 2007 in the *PNAS*. Rosi-Marshall *et al* claimed to show that pollen from Bt-maize was injurious to caddisflies in a laboratory aquatic ecosystem [17]. However, their conclusions are dubious for numerous reasons. First, pollen produced by currently available varieties of Bt-maize contains very low concentrations of Bt toxin. Second, the authors extrapolated from a laboratory experiment to a field system based on a single study, an extrapolation that is problematic, especially given that they used pollen in doses higher than the maximum encountered under field conditions. Third, and most damning of all, they reported elsewhere that they had *failed* to find these effects in the field (http://www.benthos.org/database/allnabstracts.cfm/db/Columbia2007abstracts/id/370), an important fact that should have been disclosed in the *PNAS* paper. The omission of those contrary findings arguably amounts to investigator misconduct. Fourth, earlier studies reported in the literature concluded that Bt-endotoxin concentrations in aquatic systems are extremely low and are metabolized rapidly in water [18]. Fifth, intact Bt organisms (which contain pesticidal toxins) are used to control insects by farmers and home gardeners and for mosquito abatement in ditches, ponds and lakes. Even if the authors were actually measuring the effects of Bt toxin (which is uncertain, inasmuch as they did not use isogenic lines), they appear to have had no way to know whether the toxin came from the transgenic Bt crops or whether it came from the Bt organisms applied exogenously. Sixth, the authors seem unaware that there are several variant forms of Bt endotoxin and that different Bt-maize transgenes carry different isoforms, inasmuch as there is no indication in the paper as to which they were using. Seventh, because they failed to measure the levels of Bt protein, there is no direct evidence for a dose-dependent effect of the Bt toxin. Eighth, the authors conclude that growing Bt-maize could cause downstream adverse effects in waterways, but they fail to consider alternative explanations. Under actual field conditions, any deleterious environmental effects from Bt toxin(s) (which, it should be emphasized, have *not* been demonstrated) could be derived from Bt-maize or from the exogenous application of Bt spores (*vide supra*). Finally, they analyze their results in a vacuum: in the real world, the choices are not 'Bt-maize' versus 'no intervention against pests'. The cultivation of Bt-maize could well be environmentally preferable to traditional pesticides or other strategies for controlling insects, but the authors fail to consider that possibility. Once again, we are at a loss to explain how qualified reviewers and editors could be unaware of flaws of this magnitude.

Editorial negligence or a failure of the peer review process?

Equally as shocking as the publication of such a shoddy paper in a major journal was the lack of an appropriate response from Professor Randy Schekman, the editor of *PNAS*, to numerous complaints about it (including from members of the Academy), some of them quite detailed. After promising to discuss the paper during the regular conference of the journal's associate editors, he appears to have decided to ignore the problem in the hope that it would go away. The only concession from *PNAS* was to agree to publish online a 250-word letter to the editor – along with a rebuttal of the same length from the original authors! We would remind Professor Schekman that in science, as in politics, the cover-up is often as bad as – or worse than – the original transgression.

These kinds of failures of quality control and – though we flinch at having to say it – the integrity of journals' correspondents, editors and peer reviewers inflict irreparable harm on the traditional process by which new scientific knowledge is obtained and reported. They corrupt the reporting and archiving of scientific developments for the scientific community, the popular press and the public, and they exert a broad ripple effect: within weeks of the flawed *PNAS* article being published, it was cited by European Union environmental regulators as the justification for the imposition of a ban on the sale of recombinant DNA-modified seeds [19].

Bias and negligence in the peer-review process are not, of course, limited to articles related to recombinant DNA technology. In May 2007 the journal *Cancer*, a publication of the American Cancer Society (ACS), ran a special online supplement that concluded that breast cancer is caused by trace chemicals in the environment, including pesticides, chemicals in cosmetics and substances such as PCBs and DDT [20]. As observed by Dr Elizabeth Whelan, president of the New York-based American Council on Science and Health, the paper contained several obvious, severe flaws and should not have survived peer review [21]. In addition, she pointed out the damage caused by the popular press's uncritical acceptance of the findings and that the journal and the ACS performed a grave disservice to the public. Instead of bolstering the notion that what Dr Whelan characterised as 'allegedly inescapable, invisible, hostile chemical agents' are a major cause of cancer, they should have reminded women to take prudent precautionary measures, such as regular mammograms and vaccination against human papilloma virus [21].

Ensuring the integrity of peer review

Because science is (or is supposed to be) self-correcting – a thesis is put forth, tested and ultimately revised on the basis of new data – corruption in the form of misinformation conveyed to the scientific community distorts the entire process. As Dr Whelan has pointed out (personal communication to H.I.M.), 'the peer review process is all we have in terms of quality control on what gets published. We should therefore fiercely protect the integrity of peer review. This means that the editors of these journals have the responsibility to choose the highest quality, unbiased peer reviewers – and to be alert to inherent biases.' When the editor of a preeminent scientific journal (who requested anonymity) was queried about the examples cited in this paper, he offered a similar suggestion: 'When a manuscript arrives that offers evidence bearing on a topic of intense political controversy – and the issue of risks associated with organisms modified using recombinant DNA is surely one – reviewers should be chosen who either have no recorded position on or involvement in the controversy, or who provide representation of both sides (in which case a third reviewer may have to be selected eventually!).'

More specifically, we suggest that journals should encourage their referees to ask probing, detailed questions and that the authors of the submitted article should be required to answer them to the satisfaction of the reviewers before a paper is accepted.

Had these sorts of measures been taken in the case of the research articles described above, it is unlikely that any of them would have been published in a prominent journal. But what if editors lack the courage or integrity – or simply the time – to undertake these measures? Will the scientific community take them to the woodshed? Only time will tell.

Update

On December 18, 2007, the European Food Safety Authority concluded: 'The [Scientific Panel on Genetically Modified Organisms] discussed a recently published article in *PNAS* by Rosi-Marshall *et al*., 2007 on 'Toxins in transgenic crop byproducts may affect headwater stream ecosystems' . . . In summary, the conclusions of the paper Rosi-Marshall *et al*. (2007) are not supported by the data presented in this paper. The GMO Panel is of the opinion that based on the available information such a low level of exposure to *Trichoptera* in aquatic ecosystems is unlikely to cause a toxic effect' [22].

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