of improved oversight along the entire chain of production within synthetic biology was emphasized. Increased oversight included improvements in customer and end-product screening modalities and greater cooperation between governments, industry and academics both within the US and elsewhere. Some of the AAAS participants noted that the increased financial burden required to comply with these regulations may impede private industry's investment in the technology.

Discussions at both conferences recognized that the promise of synthetic biology is associated with the potential for significant harm. There is a need to prepare for malicious acts using purely synthetic or hybrid synthetic and/or natural neo-organisms. Additionally, strategies should be in place to predict and prevent such events and to trace the source of such materials should they surface. Current prevention efforts rely on voluntary participation in a software-based matching system that checks orders against select agent sequences to head off the commercial synthesis of select agent genes, but, as the AAAS report details[4], that system could be improved.

In addition, it is imperative to identify a strong method to label synthetic genes so they can readily be identified as such. Unencrypted watermarks have already been reported in published sequences of synthetic genes (http://www.wired.com/wiredscience/2008/01/venter-institut/). Although such watermarks are feasible, currently there is a lack of regulatory controls against surreptitious insertions of sequence; synthetic genes can be tagged with DNA encoding natural amino acids, but the ability to remove, modify or even counterfeit such sequences using conventional molecular biology tools suggests that more robust strategies will be needed. One potential solution would be to create a 'serial number' that could be traced back to individual synthesis laboratories or even individual synthesis machines, and encoded into the synthetic gene using an appropriate combination of public-key and private-key hash algorithms.

Going forward, public-private cooperation will be vital for safe and effective progress within synthetic biology and to ensure that the field is not restrained by public fears. There must be a concerted effort to minimize the expense associated with regulatory compliance; however, the inherent risks of synthetic biology mandate rigorous oversight especially because the burdens of a major 'accident' will be borne by the public.

The financial expenditures that companies synthesizing genes will have to bear to proactively reduce the risk of potential misuse of the technology are substantially less than the estimated costs to respond to a biological disaster. Safety must be designed into the system and not become a secondary concern. In this respect, the attempt to shift the oversight burden from the gene manufacturers to their customers through the creation of institutional 'biosafety review boards' modeled after institutional animal care and use committees is likely to be problematic as it would further decentralize the review process and rely on committee structures that were not designed to preemptively detect hazardous modalities.

The AAAS[4] and NAKFI-SB[5] meetings were an excellent starting point for debate and we strongly recommend that the discussions be expanded and that the subsequent safety recommendations become expeditiously implemented.

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The regulatory bottleneck for biotech specialty crops

To the Editor:

Specialty crops, which include fruits, vegetables, nuts, turf and ornamental crops, are important components of human diets and provide environmental amenities[1]. In 2007, such crops represented ~40% of the $140 billion in total agricultural receipts, despite being cultivated on just 4% of the total cropped area[2]. Although tomato was the first genetically modified (GM) food crop to be commercialized in 1994, the only GM specialty crop traits currently marketed are virus-resistant papaya and squash, insect-resistant sweet corn and violet carnations. All of these received initial regulatory approval over 10 years ago. As a group, GM specialty crops have garnered limited market share (the exception is GM papaya resistant to papaya ringspot virus[1], which now produces 90% of Hawaii's crop). In contrast, GM field crops, such as soybean, maize, cotton and canola, have come to dominate the markets in countries where they have been released[3]. What is responsible for this disparity in the commercialization of GM field crops versus specialty crops?

One possibility is that the dearth of GM specialty crops indicates a lack of current research or of beneficial traits for crop improvement through genetic engineering. Alternatively, research may have continued but progression through the regulatory process to the marketplace may have failed. Anticipated lack of market acceptance could have stopped either research or regulatory submissions. To find out why specialty crops with GM traits have fared so poorly, we have analyzed the research, regulatory and market pipeline to determine which steps in the process may be responsible for the limited range of commercially available products.

To assess the recent research and development pipeline for GM specialty crops, an extensive search was conducted on a global scale for scientific journal articles, describing work in specialty crops using recombinant DNA (transgenic) methods, published between January 2003 and October 2008 (**Supplementary Table 1**). In most cases, these reports demonstrate proof of concept of the effectiveness of the transgene in producing the phenotypic trait in the species studied. Among 313 published articles on specialty crops, 46 species were represented, of which tobacco, potato and tomato accounted for 59% of the total reports, in part due to their use as easily transformed

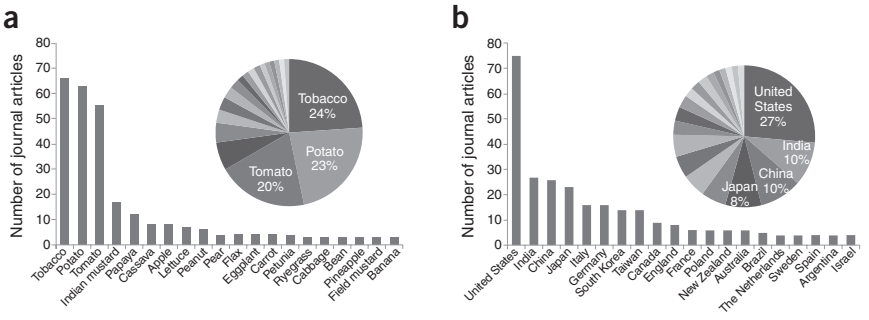

Figure 1 International scientific journal publications on transgenic crops. (**a**) Number of published articles describing research on the top 20 GM specialty crops (of 46 total species). The percentage of reports on each crop is also shown (inset). (**b**) Number of published articles according to country of origin. The percentage of total articles by country is also shown (inset). A complete list of all publications is in **Supplementary Table 1**.

model plants in research laboratories (**Fig. 1a**). Although the United States is the leader in the number of articles published, many reports originate from the European Union (EU; Brussels), India, Japan and China (**Fig. 1b**). Other plant biotech surveys also indicate that a number of GM specialty crops are being developed in China[4,5].

Following laboratory studies and proof of concept, development of GM crops generally proceeds to field trials. Because countries began establishing their independent regulatory processes specifically for GM organisms beginning in the early 1990s, thousands of field trial permits have been granted worldwide. The Organization for Economic Co-operation and Development (OECD; Paris) developed the UNU-MERIT field trial database, which collates GM trials that are ongoing in 24 developed countries, although data for China and India are not included (A. Arundel, OECD, personal communication). During this six-year period (2003–2008), the United States accounted for ~70% of all field trials, with 15% of the total field trials being conducted on specialty crops (**Fig. 2a**). The United States and Canada were responsible for 88% of the 1,231 permitted field trials on specialty crops, with the majority of the Canadian trials focused on mustard crops. The Information Systems for Biotechnology database (http://gophisb.biochem.vt.edu) was also queried to identify all approved field test permit applications in the United States between 1992 and October 2008. Field trials of specialty crops averaged 39% of the number in commodity crops from 1992 to 2002, but only 18% since 2003 (**Fig. 2b**). Qualitative data on GM crops under development internationally confirm that although laboratory and field trials have been conducted on GM specialty crops in many countries, none has progressed to commercial production outside the United States, except perhaps virus-resistant tomato and pepper in China, the commercial status of which is currently uncertain[6,7].

To further evaluate the scope of research that has been conducted on GM specialty crops, we categorized the traits from scientific reports and field trials into two categories: output traits, which would directly benefit consumers; and input traits, which primarily benefit producers and only indirectly benefit consumers through reduced agricultural inputs, higher productivity, lower cost or reduced environmental impacts. This compilation identified 77 specialty crops (listed in **Supplementary Table 2**) and 260 unique traits (**Supplementary Data** and **Supplementary Table 1**). The output traits included modifications in oil, sugar and starch content, protein quality and amino acid composition, vitamin content and nutritional quality, flavor and postharvest quality as well as reduced allergenicity. Input traits included tolerance to abiotic and biotic stresses, insect and nematode resistance, herbicide tolerance, nitrogen acquisition and yield. These data demonstrate that there is a broad global research pipeline for GM specialty crops using traits that would be beneficial to both producers and consumers.

Governmental approval is required before GM crops can be marketed. Since 1992, 24 governmental bodies have approved or deregulated a total of 84 unique plant and trait combinations (http://www.cera.gmc.org/). Regulatory approvals of GM specialty crops averaged 48% of the number in commodity crops from 1992 to 2002, but only 5% since 2003 (**Fig. 2c**). Although 21 approvals have been granted by all governmental bodies for nine specialty crops, only two have occurred since 2000. These two transgenic events are reduced nicotine content in tobacco and virus resistance in plum. The tobacco product was marketed briefly in the United States as an aid to smoking cessation, and the GM plum variety still awaits final approval from the US Environmental Protection Agency before it can be grown commercially.

The distribution of all regulatory approvals exhibits two distinct phases (**Fig. 2c**). Approvals initially peaked in 1995, followed by a decline to only one approval each in 2000 and 2001. The number of approvals then increased, albeit slowly, but only for commodity crops. A recent analysis shows that innovations in agbiotech were on an exponentially increasing trend during the 1990s, which then abruptly leveled off around 1998, with a decline in subsequent years[8]. Furthermore, new innovations entering the pipeline after 1998 were less likely to move toward commercialization. These patterns were attributed to a global change in regulatory and market policies toward GM crops, notably the moratorium on new approvals and therefore marketing in the EU beginning in 1998. Our results indicate that in contrast to the pre-1998 era, only commodity crop developers were able to participate successfully in this new regulatory and market environment.

There are a number of possible reasons why GM specialty crops are not progressing past the research phase, and exploring these deserves further research. Previous analyses have documented that the $1–15 million in additional costs per insertion event associated with receiving regulatory approval[9,10] (which is not required for varieties developed using other breeding methods) are out of proportion to the potential additional market value that can be recovered on the limited areas devoted to these crops[11]. Similarly, a review on ornamental specialty crops concluded that although there is considerable technology available and valuable traits to be exploited, GM varieties are still unattractive from an economic perspective, primarily due to regulatory costs[9].

Lack of demand or market rejection of GM specialty crops could also be the reason for their absence. This is undoubtedly the case in some countries and markets that unconditionally ban GM products, but the hypothesis is difficult to test, as until they receive regulatory approval, GM products

are not available for consumers to accept or reject. For example, although Indian Minister for the Environment Jairam Ramesh cited a lack of public confidence when he recently blocked regulatory approval of insect-resistant GM brinjal (eggplant)[12], his action precluded consumers from having the opportunity to demonstrate their preferences in the marketplace. Given the limited number of GM specialty crops that have received regulatory approval, consumer acceptance remains largely untested in the market. Our interviews with specialty crop seed companies and nurseries provide extensive anecdotal evidence that many potentially marketable GM products have been created and tested in the private sector, but the cost and uncertainty of the regulatory process has made further development uneconomical and prevented them from testing actual market acceptance.

The justification for requiring costly regulatory testing of GM plants is to ensure that potential risks are fully assessed before commercial release. Thus, it can be argued, if specialty crops cannot meet this standard economically, that is the price to be paid to eliminate risk. However, even virtually identical traits do not require such approval if developed using non-GM methods and no actual risks unique to the recombinant DNA process *per se* have been experienced with the GM crops currently marketed. On the other hand, the constriction in commercialization of GM traits has resulted in lost societal benefits due to foregone innovations that are estimated to be in the billions of dollars[10,13]. When GM crops could reduce environmental impacts or improve health and nutrition relative to current varieties (**Supplementary Data**), failure to use them also constitutes risks that generally are not considered in regulatory evaluations[14]. Although research on GM specialty crops continues to explore a wide range of input and output applications, their commercialization may depend upon a reexamination of the balance between potential risks versus foregone societal benefits and consequent adjustments in regulatory requirements.

Note: Supplementary information is available on the Nature Biotechnology website.

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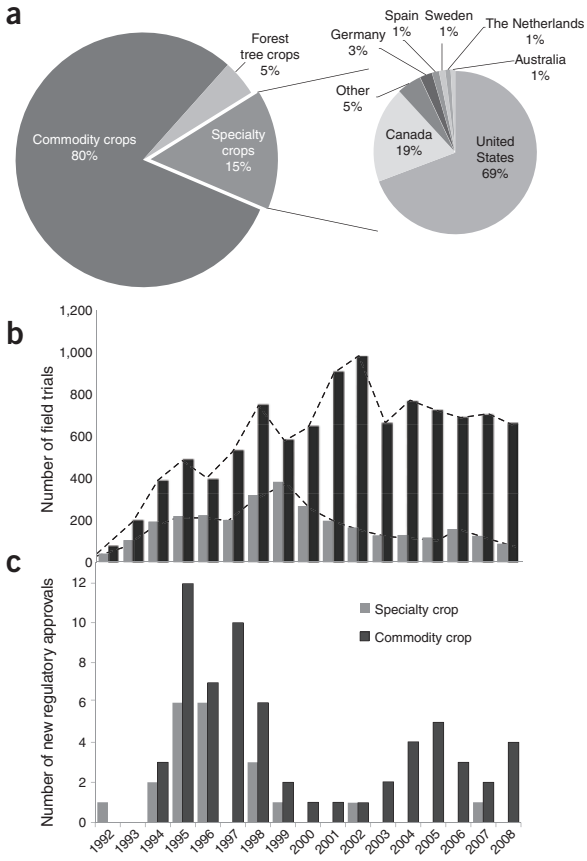

Figure 2 Field trials and regulatory approvals. (**a**) Using the UNU-MERIT database, field trials conducted in 24 developed countries between 2003 and 2008 were separated on the basis of commodity, forest tree or specialty crop. From this, the specialty crops were further subdivided based on the country in which the field trial was conducted. (**b**) The numbers of field trial permits acknowledged or issued in the United States are plotted by year for commodity crops and specialty crops. (**c**) The 84 unique transgenic events that have been granted regulatory approval by one or more countries are plotted by year of approval. If the year of approval varied among countries, the first year of regulatory approval granted by any agency for a given event was used.

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