The contraction of agbiotech product quality innovation

To the Editor:

Agbiotech innovations that directly benefit users beyond the farm gate—such as nutritional content, ripening control or processing characteristics—have not been commercialized to nearly the same extent as pest-control traits like insect resistance and herbicide tolerance. Product quality or 'output' traits have been anticipated since the earliest days of plant genetic engineering[1]. They are expected to improve public perceptions of genetic engineering[2,3] and make agricultural and natural resource systems more responsive to environmental demands[4]. The question thus stands: Why have quality-improving innovations from agbiotech not been more readily forthcoming?

Here we address this question through two surveys of the global R&D pipeline, which were undertaken to determine the extent to which product quality innovations have been moving toward commercialization and, thereby, to explore what factors may be affecting the development of this type of application of plant biotech. The primary survey was backward looking, drawing upon published records to reconstruct the histories of 558 product quality innovations (**Table 1** and **Supplementary Table 1**). Three common denominators—(i) the plant species, (ii) the trait and (iii) the innovating organization—were used to define a single 'innovation'. Once identified, a single innovation's development was traced through the various stages of R&D by collating multiple records including scientific articles, field trials and/or regulatory filings that refer to the same innovation. For example, all records of (i) maize (ii) with increased lysine (iii) by the University of Minnesota (St. Paul, MN, USA) were combined to trace the history of that innovation. (For more details, see **Supplementary Notes.**)

A second survey was undertaken that was forward looking, collecting predictions from agbiotech companies and industry analysts about future product commercialization. It identified 49 quality innovations expected by 2015 (**Table 1** for a summary and **Supplementary Table 2** for full data.) In comparing the 558 innovations in the primary survey to the 49 in the secondary survey, we note that about three quarters of the 558 had already been discontinued and only a portion of those remaining were mature enough to warrant an expectation of commercialization. Thus, the 49 innovations identified in the secondary survey are likely a good representation of what is indeed forthcoming.

The results of these two surveys illustrate the typical filtering or screening function of the R&D process, whereby unsuitable candidates are culled from further development based on technical, safety and economic criteria. Of the 558 innovations identified in the primary survey (**Table 1**), 355 had entered initial field trials; of those, 51 had gone on to advanced field trials; 14 were submitted for regulatory approval and five were actually commercialized. Only two remain on the market (a mauve carnation commercialized in Australia and Asia and a reduced nicotine cigarette in regional test markets in the United States).

Of the 49 product candidates identified in the secondary survey (**Table 1**) very few had been submitted for regulatory approval. Further attribution during regulatory review and commercialization will probably mean only a fraction of these 49 reaches market.

Activity has been uneven across the ten identified trait categories (**Table 1**). Traits governing content and composition of macronutrients—proteins, oils and carbohydrates—and traits that control fruit ripening have reached later stages of R&D, whereas fewer products with enhanced micronutrients, functional food components or novel esthetics are expected (as shown in a secondary survey).

Product quality innovation appears to be responding more to demand in intermediate markets for processing and feed attributes than to demand in final retail markets for improved or novel products. Of the 558 innovations identified

Table 1 Surveys of actual and expected progress in ten categories of transgenic product quality innovations

Trait category	Primary survey[a]: Highest stage attained: Publication only	Field trials: Initial (1–3)	Field trials: Mid-stage (4–9)	Field trials: Late-stage (≥10)	Regulatory	Commercialized	Total	Secondary survey[b]: Expected commercialization: By 2010	2010–2015	Total
Proteins and amino acids	33	47	12	7	1	0	**100**	8	6	**14**
Oils and fatty acids	15	22	8	5	2	1	**53**	4	4	**8**
Carbohydrates and sugars	32	65	16	10	0	0	**123**	2	1	**3**
Vitamins, minerals and functional components	47	15	3	1	0	0	**84**	0	2	**2**
Reduced nonnutrients, allergens or toxins	18	6	0	2	0	1	**9**	3	0	**3**
Ripening, freshness or shelf life	19	41	10	6	5	2	**83**	4	3	**7**
Esthetics and convenience	15	21	5	2	1	1	**43**	0	3	**3**
Fiber quality for digestibility and pulping	22	16	5	1	0	0	**44**	5	1	**6**
Plant bioremediation	2	8	0	0	0	0	**12**	0	0	**0**
Multiple or unspecified quality traits: 'seed composition' and 'feed quality'	0	2	2	3	0	0	**7**	2	1	**3**
Total	**203**	**243**	**61**	**37**	**9**	**5**	**558**	**28**	**21**	**49**

[a]The primary survey combined records from scientific publications, field trial records and regulatory filings to identify 558 transgenic plants with quality improvements and determine how far they had progressed through stages of R&D by 2004, including those that had only been published in the scientific literature; those that had reached initial field trials (defined as having completed 1–3 field trials), mid-stage field trials (4–9 field trials) or advanced field trials (>10); those that had entered regulatory filings; and those that were commercialized. [b]The secondary survey canvassed expectations of firms and analysts about the likelihood and time frame for future commercialization of transgenic product quality innovations. Complete one-to-one correspondence between individual observations of the two surveys was not possible.

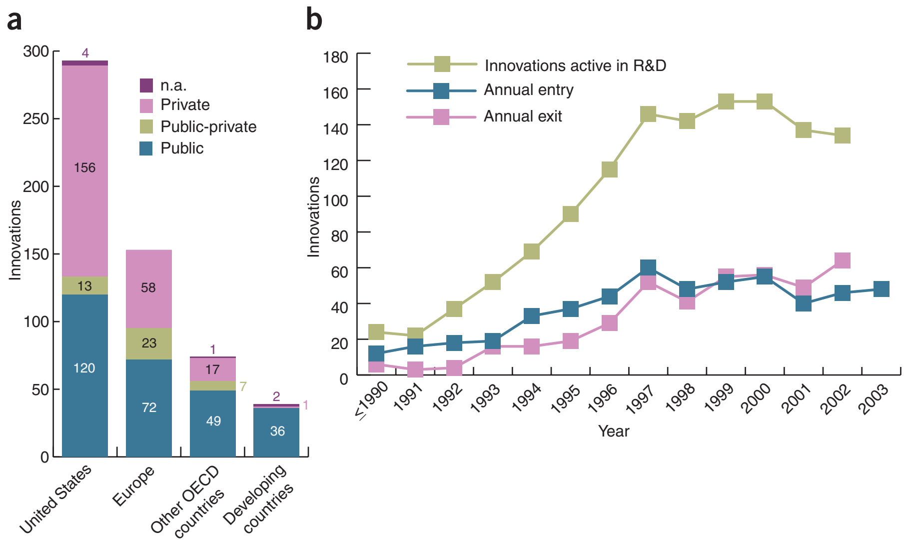

Figure 1 Innovation in agbiotech. (**a**) Location and sector of organizations conducting R&D for the 558 transgenic product quality innovations identified. Private sector consists of corporate and privately held firms. Public sector consists of government research laboratories, universities and nonprofit research institutes. (**b**) Annual entry, exit and the numbers of innovations active in the R&D pipeline were calculated from observations of the 558 innovations tracked in the primary survey. The number of active innovations stopped growing in 1998, after which those new innovations that entered were more likely to be published and less likely to move toward commercialization.

in the primary survey, 53% are for food processing or animal feed, 23% are for final consumers and another 23% are likely useful to both.

Many of the observed traits offer potential efficiency gains in agricultural and natural resource systems, reducing environmental impacts on the margin both by decreasing input requirements and by reducing negative externalities of crop production, processing or consumption. For example, a significant impact could result from increased nutritional efficiency of animal feeds by, for example, easing land and water resources required for feed production and reducing the offload of excess nutrients like phosphorus and nitrogen in animal waste. Major impacts could also result from increased digestibility of plant fibers, by reducing chemical and energy inputs required for pulp and paper manufacture as well as for the emerging production of cellulosic biofuels.

Product quality innovations are advancing in many countries, in both the public and private sectors (**Fig. 1a**). More than half of the observed innovations arose in the United States, 28% in Europe, 13% in other Organization for Economic Cooperation and Development (OECD; Paris) countries (particularly Japan, Australia and Canada), and 7% in developing countries (particularly India, South Africa, China and Malaysia). In the Unites States, the private sector accounts for over half of the innovations in the pipeline; in Europe, just over a third; in other OECD countries, less than a quarter; and in developing countries, virtually none. Overall, the share of R&D activity in the private sector is correlated with the absolute level of activity in the public sector, suggesting that public and private sector R&D mutually reinforce each other in a country's capacity for commercial innovation.

In general, dynamic models of innovation[5,6] suggest an S-shaped growth curve is followed in the development of a new field of technology, consisting of an early breakthrough phase, followed by a takeoff or growth phase in which there is rapid acceleration, a slowdown phase as the technology matures and an eventual decline phase. These phases reflect interacting processes of discovery, refinement, diffusion and obsolescence that can stretch over decades. Because the genetic engineering of agricultural quality attributes was clearly in its infancy in the late 1980s, it is reasonable to assume that the field entered its growth phase sometime in the early 1990s, that the rate of innovation would have continued to increase for some time and the rate of innovations entering market would have grown.

Indeed, the survey identifies early breakthroughs in the 1980s in flower pigmentation and fruit ripening control.

There was a clear growth phase through the early and mid-1990s (**Fig. 1b**). Rather than continuing the acceleration typical of a growth phase, however, innovation appears to level off around 1998. Three lines of evidence suggest this is a departure from the expected pattern (see interpretation of results in **Supplementary Notes**.) First, regression analysis shows that innovations active in the R&D pipeline were growing at an increasing rate during the period before 1998, but declined after 1998. Fitting the data to a quadratic structural equation gives statistically significant coefficients of opposite signs for these two periods, indicating a break around 1998 at which the original upward trend turns down (**Supplementary Notes**). Second, although the probability of reporting an innovation in a scientific journal increased after 1998, the probability of advancing an innovation through field trials and on to market decreased. At the same time, those innovations that entered after 1998 advanced through R&D at least as quickly as those that had entered before 1998 (**Supplementary Notes**). Individual innovations are therefore not merely being drawn out over longer time horizons; they are failing to advance to the later stages of R&D. Third and finally, the surveys show that, although only four innovations had reached the market by 1998, 130 innovations were still in the pipeline, only one additional product reached market after 1998. This reduction in commercialization events, despite a previously full R&D pipeline is not characteristic of a typical S-curve slowdown due to technology maturity, let alone a downturn due to obsolescence.

The contraction in product quality innovation indicated by the above analysis is consistent with observations in the literature that overall numbers of transgenic field trials conducted in the Unites States and Europe declined in the late 1990s[7]. It also coincides with the exit from agbiotech of several smaller biotech companies and food manufacturers who were not deeply invested in the technology's 'first generation' of pest control applications (**Supplementary Notes**).

These trends may be related to several technical and economic factors that have been discussed widely in the academic and trade literatures, given that decisions to continue or cancel R&D projects hinge on whether expected returns justify continued expenditures. Changes can affect either expected returns or expenditures. Technically, traits governed by single genes were relatively easy to exploit, but as more complex nutritional and quality traits involving greater complexities in gene expression were pursued, these likely were more difficult or costly to develop[8]. Legally, the difficulty and cost of navigating access to essential 'enabling' intellectual property probably increased as more technologies came under patent[9]. Expected economic returns from transgenic quality innovations may have declined due to competition from reasonably close nontransgenic substitutes, such as bred varieties of fresh tomatoes. Expected demand for transgenic products may have been tempered by growing consumer uncertainties over food uses of biotech, intensified media-focused activism or key public decisions by major institutional buyers like McDonald's.

Although the above factors contributed to the slowdown, the one factor that is presumably most closely related to the observed drop in innovation after 1998 was the halting of regulatory approvals in Europe in 1998 and its repercussions with regulators in other countries[10]. This suggests that regulatory responses, largely directed at controlling risks of 'first-generation' pest control biotechnologies, may have contributed to a slowdown in developing 'second-generation' product quality biotechnologies: a slowdown that ultimately could prove to have significant and lasting social welfare costs in terms of delayed or foregone innovation in nutrition, production efficiency and environmental mitigation.

In summary, then, the surveys reported here find that a wide array of product quality innovations have been in the agbiotech R&D pipeline. Even so, the data reveal a significant structural shift in the rate of R&D around 1998. Although the causes and impacts of such a slowdown are conjectural, the coincidence of the date suggests that changes in the regulatory environment may have been a cause. The potential welfare-enhancing nature of some of these undeveloped traits warns of potential social costs from foregone innovation.

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

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