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OPINION PAPER

Global regulatory burden for field testing of genetically modified trees

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Abstract Field trials are widely known to be essential for understanding the value and adaptability of trees produced via conventional and transgenic biotechnologies. However, obtaining permission for transgenic field trials is often considered to be very difficult in many countries. To understand the extent of regulatory requirements around the world and the burdens they impose, we surveyed 36 scientists and practitioners from 20 different countries who had experience or direct knowledge of regulatory compliance with field trials of transgenic trees. Results showed that permits and monitoring were universally required, and that public disclosure of field trial locations was required in three quarters of countries. Other major findings were that: separate approvals for different constructs, tree species, and trial locations were required in more than three quarters of the countries; characterization of each transgene insertion event was required as part of the application in four fifths of countries; and the application process itself was perceived as the largest single burden. Regulatory tiers that differentiate different kinds of transgenic trees based on perceived risk were present in only one fifth of countries. The data confirm the widespread perception among scientists that the costs and burdens of conducting field trials with transgenic trees are nearly universal substantial impediments to scientific and breeding progress.

Keywords Genetically modified trees · Genetically engineered trees · Forest biotechnology · Cisgenic · Intragenic · Forest plantations

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Introduction

Field trials with transgenic trees (often called genetically modified or GM trees) have been carried out for more than 20 years (Valenzuela et al. 2006; Robischon 2006). Tests have been conducted in several countries, including Australia, Belgium, Brazil, Canada, China, France, Finland, Germany, Italy, Japan, New Zealand, Norway, Portugal, Spain, Sweden, The Netherlands, UK, and USA (Office of the Gene Technology Regulator 2011; National Technical Biosafety Committee 2011; Canadian Food Inspection Agency 2011; Ewald et al. 2006; Institute for Health and Consumer Protection (European Commission Joint Research Center) 2011; Japan Biosafety Clearing House 2011; Environmental Protection Authority 2011; and Information Systems for Biotechnology 2011). Despite the widely agreed importance of field trials for obtaining ecologically and economically relevant trait data (Strauss et al. 2009a), and an absence of any documented releases or ecological harms from field trials (Walter et al. 2010), regulatory barriers to field trial permits appear to be growing larger, not smaller (Strauss et al. 2009a).

More than 700 field trials of GM trees were recently reported from a search of publicly accessible databases (Walter et al. 2010). A wide diversity of sources of

transgenes and regulatory elements, and intended traits, have been tested, including expression of reporter genes; insect, disease, and herbicide resistance; modified wood properties; modified flowering and fertility; and modified growth rate and stature (reviews in Neale and Kremer 2011; Ahuja 2011; Harfouche et al. 2011; Grattapaglia et al. 2009; Poupin and Arce-Johnson 2005; Boerjan 2005).

Despite the potential for long distance gene flow from pollen or seeds, GM forest trees are easier to contain during research than many annual crops. This is because the trees are usually cut back, or the trials terminated, prior to the onset of flowering. Thus, for routine research field trials of GM forest trees, their innate juvenile sterility facilitates containment and thus regulatory compliance. Nonetheless, even in the USA, where regulations are widely considered to be less stringent than in Europe and Japan, scientists perceive regulatory requirements to be a substantial burden. In a recent survey of forest scientists conducted in the USA, more than 75% of the respondents felt that regulatory requirements posed a "substantial obstacle" to field research on GM trees (Strauss et al. 2009b).

Field trials are widely regarded as essential for breeding and ecophysiological studies; artificial environments do not effectively rank superior varieties nor do they induce normal plant physiologies. This is likely to be because the plants are exposed to multiples stresses in the field that vary in duration and intensity in a manner that cannot be duplicated in controlled environments (Laurentius et al. 2008). Thus, artificial environments can give highly misleading impressions of the effects of GM traits for basic scientific, biotechnological, and breeding studies (Voelker et al. 2010; Zeller et al. 2010). This is especially true in the case of complex traits such abiotic stress tolerances (e.g., Campos et al. 2004; Brunetti et al. 2011; Euliss et al. 2008).

Unfortunately, direct comparisons of field vs. greenhouse or laboratory results are rare, so the difference in performance is often unappreciated. Recent comparative studies of genetically caused phenotypic variation between European Aspen (*Populus tremula*) ecotypes (Luquez et al. 2008) in the greenhouse and two field environments illustrate the extent of physiological differentiation (Fig. 1). When two major classes of leaf phenolics that play critical roles in stress tolerance and herbivore interactions were studied, the differences between the greenhouse and field environments were striking. Moreover, there was also large variation among the two field sites, showing that not one, but multiple field environments, are needed to understand the extent of ecotype-associated phenotypic variation. Thus, regulatory obstacles that impede field studies, or cause them to be restricted to only single environments, will prevent scientifically informative economic and biosafety studies.

To try to obtain a global picture of the state of regulation and their perceived burdens to scientists conducting them, we polled scientists that we identified based on the literature, attendance at international meetings, and directed web searches. The scientists that were selected had conducted GM tree field trials or had direct knowledge of regulatory practices that would apply to their conduct. We also used these scientists to inform us of others in countries that we had missed and contacted them. Because it is difficult to ascertain the actual burden from written regulations—whose implementation is often dictated by undocumented bureaucratic and political influence—we relied solely on poll responses. Because this field of study is small, and a limited number of public sector scientists and countries have recently conducted field trials with GM trees, we believe that we have obtained responses from a majority of investigators and countries that have recently conducted field trials of GM trees.

Methods

Email invitations to take part in the survey were sent to 103 scientists between 21 April and 19 May 2010. The first part of the survey asked about the state of regulations, for which only a single response per country was used for tabulating responses. For the second part of the survey, which asked about perceived regulatory burden, all responses were used in tabulations. The online survey was implemented using a software developed by the Business Solutions Group at Oregon State University (http://bsg.oregonstate.edu/projects). The full survey is provided in electronic supplementary Appendix S1; the responses to questions 17–42 can be found in electronic supplementary Table S2, while the responses to other questions, except questions 49–56, can be found in electronic supplementary Table S3. The responses to questions 49–56 can be found in electronic supplementary Table S4.

Results and discussion

Of the103 scientists contacted, a total of 36, representing 20 different countries, responded. The countries with responding scientists included Austria, Belgium, Brazil, Canada, Chile, China, Finland, France, Germany, Hungary, India, Italy, Jamaica, Japan, The Netherlands, New Zealand, Nigeria, Spain, Sweden, and the USA. The continents of North America and Europe were represented by 12 and 13 scientists, respectively. All but three of the responding scientists had PhDs, with the others having a master's degree. More than 85% of the scientists worked in public sector institutions. Nearly one half of the scientists surveyed worked on *Populus*, and the top three major

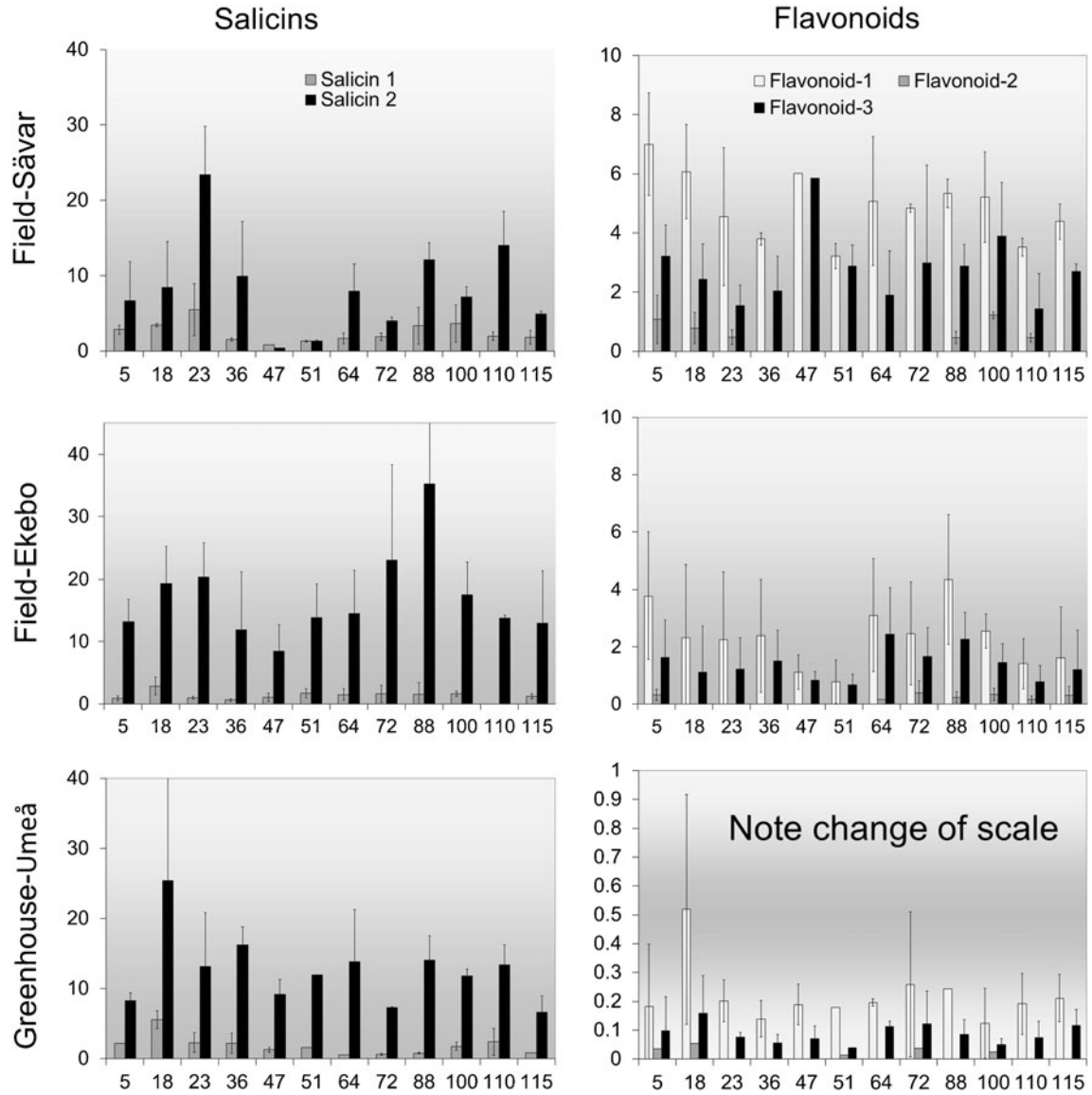

Fig. 1 Biochemical variation among greenhouse and field environments. Differences in production of salicins (*left*) and flavonoids (*right*) among vegetative clones of 12 wild aspen genotypes grown in the greenhouse (*bottom two figures*) and trees grown in a common garden experiment in two different locations in Sweden (Ekebo—*middle two figures*, and Sävar—*top two figures*; Abreu and Albrectsen, unpublished). The *y*-axis indicates area of peak absorbances in the chromatograms, adjusted for sample concentration in the extract (in ten thousands for the salicins, and part per million for the flavonoids). The *x*-axis is tree clone ID

research objectives they reported were disease resistance, bioenergy, and wood quality. About 80% of the scientists had personally conducted at least one field trial with transgenic trees, and five scientists had conducted more than 20 field trials.

The first part of the study, which asked about the state of regulations, showed that submission of sufficient information to obtain a field trial permit, and basic reporting requirements, is difficult in many countries. In no cases were GM trees exempt from the need for a permit or the need for monitoring after permission was granted, and in all but one case, monitoring after removal of the trial was required (Table 1). In three quarters of countries, disclosure of the field site to the public was mandatory, a condition that has clearly facilitated vandalism against field sites in Europe. In only one fifth of countries were there tiers of scrutiny established for regulation; in all cases, these were for higher risk rather than lower risk tiers, such as for GM trees with genes for bioindustrial or bioremediation purposes. Cisgenic or intragenic genotypes (composed of genes from sexually compatible species: Schouten and Jacobsen 2008; Viswanath and Strauss 2010), or those with domestication phenotypes (Strauss 2003a), were not regulated less stringently. The governments in more than half of

Table 1 Summary of selected responses

Question	Number of respondents who answered "YES"	Number of respondents who answered "NO"
Mandatory disclosure of field site locations (17)	15 (75%)	5 (25%)
Presence of regulatory tiers (19)	4 (20%)	16 (80%)
Exemption from field trial regulation (21)	0	19 (100%)
Application fee (24)	11 (61.11%)	7 (38.89%)
Characterization (26)	16 (80%)	4 (20%)
Fencing/trenching (28)	12 (63.16%)	7 (36.84%)
Monitoring and reporting (30)	20 (100%)	0
Approvals for different locations (34)	14 (77.78%)	4 (22.22%)
Approvals for different constructs (35)	15 (78.95%)	4 (21.05%)
Approvals for different tree species (36)	16 (88.89%)	2 (11.11%)
Approvals for different gene insertions (37)	4 (26.67%)	11 (73.33%)
Monitoring after removal (38)	18 (94.74%)	1 (5.26%)
Requirements for special disposal of dead transgenic tissue (41)	5 (45.45%)	6 (54.55%)

The question number (see supplementary Table S1) is indicated in parentheses

the represented countries charged a fee for application processing, with application fees ranging from US $100 to $25,000 per permit. A majority of countries required fencing and/or trenching (Table 1). We asked whether a single permit could cover a number of constructs, events, tree species, and/or field sites, or if these would require separate applications. In about 80% of the cases, separate permits were required for different constructs, locations, and tree species, and separate permits for independent gene insertions with the same construct were required in 30% of the cases. Five of 11 respondents reported that dead materials cannot be disposed off like other biomass but require special procedures such as burning or deep burial.

About one third of scientists from North America, mostly the USA, believed that regulations deterred field research with GM trees, similar to that in Asia and about half that of Europe (Fig. 2a). Likewise, very few scientists in the USA or in Asia were concerned about ecovandalism as a serious risk (large majority below 10% biannual risk), though the risk was considered to be above 50% by about one third of the European respondents (Fig. 2b). The added annual field trial costs for compliance with regulations was lowest in Asia (large majority below US $10,000) and highest in the USA (half of respondents rated it above US $10,000) (Fig. 2c). Characterization of each transgene insert prior to issuing a field trial was required in 80% of the countries (Fig. 3a), though the specific molecular studies required varied. Although PCR, with suitable controls, is sufficient to establish transgene presence in the genome, most countries required comparatively laborious Southern blots and insert sequencing (Fig. 3b), even though there is no clear relationship between ecological risk from a field trial and such molecular knowledge. Because phenotypic variation among insertion events is often very large, requiring study of tens to dozens of events per construct for meaningful scientific inferences, this burden, plus the need for separate applications in nearly one third of cases, will directly compromise studies by forcing the use of one or very few events and constructs. Thus, it is no surprise that the initial application step was perceived as the most cumbersome step in field testing (Fig. 3c). The long time for approval, particularly in Europe and Asia, often due to political and public interest group interference in decision-making, is also likely to be a contributing factor to this perception (Fig. 3d). One respondent from Europe commented that "Many times the local politicians … have strong scientific or technical opinions … It can take many months or even more than 1 year to get an answer…"

Conclusion

Our survey shows that regulations on GM trees impose substantial burdens. These include: uncertainties in approvals and the time period to obtain permission; several years of monitoring following harvest to detect root sprouts or seedlings; added costs of molecular characterization and permit preparation even for familiar types of genetic modifications; special disposal procedures for large amounts of tree biomass; and the risks of loss due to vandalism as a result of site disclosure requirements. It follows that many scientific studies are likely to never be undertaken, and the quality of studies that are done will frequently be of reduced quality due to reduced size and scope. These conditions clearly impede science and technology development.

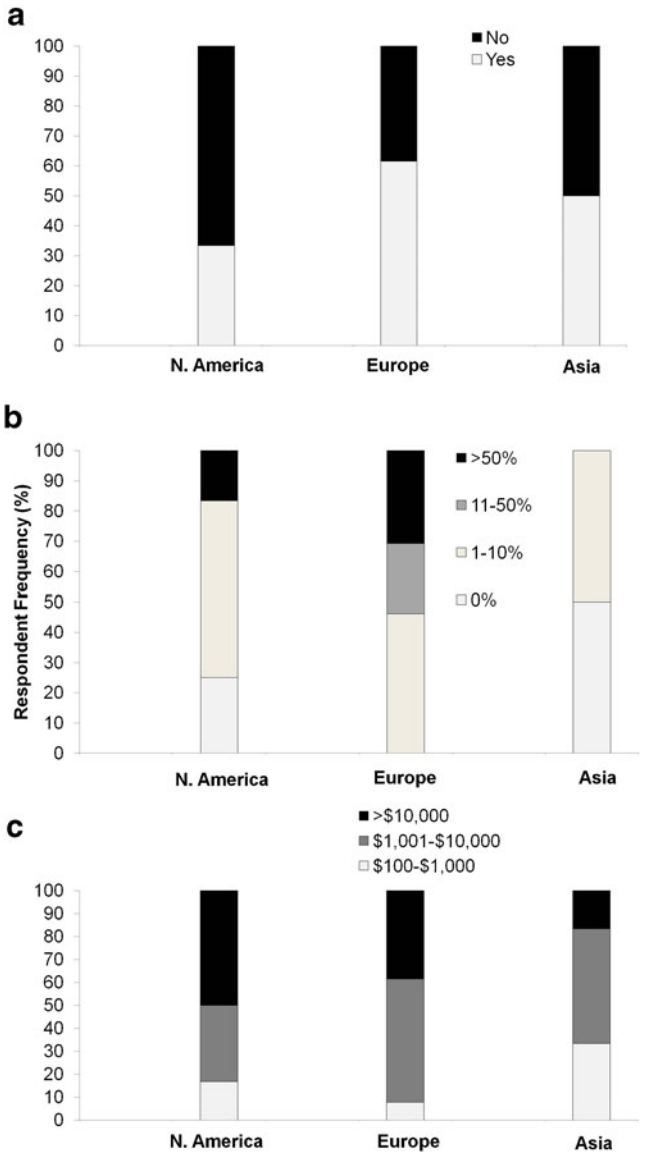

Fig. 2 Effect of regulations on deterrence of field research. **a** The proportion of scientists that felt the stringent regulations in their country deterred field research on GM trees was higher in Europe and Asia, when compared with North America. **b** Likelihood of at least one vandalism event occurring during a 2-year trial of GM trees was estimated to be higher in Europe, when compared with North America and Asia. **c** A high proportion of scientists in North America and Europe felt that annual costs for regulatory compliance exceeded US $10, 000

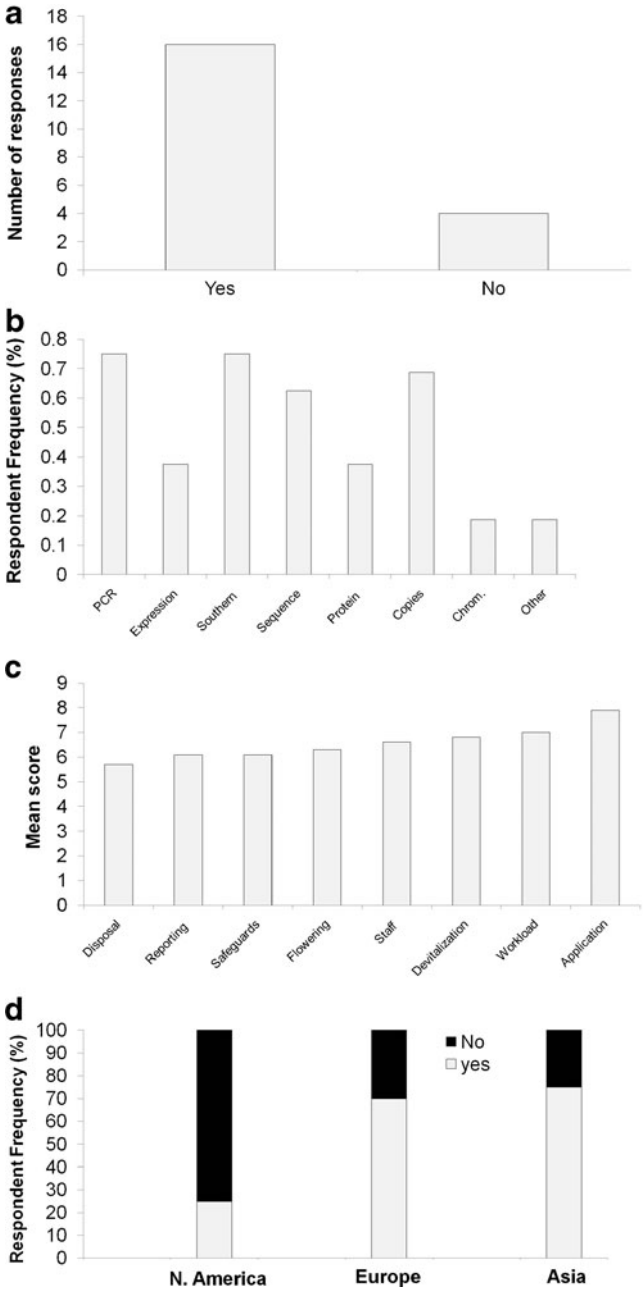

Fig. 3 Requirements and obstacles for GM field trials. **a** Characterization of the insert is not required in only four (Canada, Sweden, The Netherlands, and USA) out of the 20 countries represented in the survey. **b** Most of the countries require in-depth molecular characterization of inserted genes. **c** The initial application process was deemed to be the most cumbersome step in a GM field trial compared with a field trial of non-GM trees. **d** A majority of scientists (>70%) in both Europe and Asia felt the decision-making process to approve a GM field trial is political

We therefore believe that policy changes to reduce these burdens for research should be a high priority and urgently considered by influential global institutions such as the Convention on Biological Diversity (Strauss et al. 2009a), as well as by national regulatory agencies. Detailed suggestions for modifications to regulations to make them less onerous to researchers have been widely discussed elsewhere (e.g., Strauss 2003b; Bradford et al. 2005; Strauss et al. 2010). They include exclusion of the need to disclose precise field trial locations; exclusion of requirements for public participation about approval decisions for contained trials; exclusion of detailed characterization of insert structure and expression; exemptions for cisgenic and intragenic genotypes; exemptions for widely studied and

familiar types of transgenic sequences (e.g., selected reporter and selectable marker genes, promoters, terminators, and vector sequences); exemptions for required data related to mutagenesis-associated effects, as such effects are also present with many conventional breeding methods; exemptions for transgenes where there is no significant likelihood that fitness of associated wild or feral plants will be increased; and institution of "best management practices" (Strauss et al. 2010) rather than strict permitting, monitoring, and associated legal liabilities for gene dispersal of all but high-risk transgenes. We believe that through such changes, a much wider diversity of field research is likely to be undertaken while also providing a very high degree of environmental protection. The net result is likely to be wider use of transgenic methods to improve the economic value and environmental safety of intensively bred, exotic, and transgenic tree crops.

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