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Global Adoption of Genetically Modified (GM) Crops: Challenges for the Public Sector

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ABSTRACT: Advances in biotechnology continue to drive the development of a wide range of insect-protected, herbicide-tolerant, stress-tolerant, and nutritionally enhanced genetically modified (GM) crops, yet societal and public policy considerations may slow their commercialization. Such restrictions may disproportionately affect developing countries, as well as smaller entrepreneurial and public sector initiatives. The 2014 IUPAC International Congress of Pesticide Chemistry (San Francisco, CA, USA; August 2014) included a symposium on "Challenges Associated with Global Adoption of Agricultural Biotechnology" to review current obstacles in promoting GM crops. Challenges identified by symposium presenters included (i) poor public understanding of GM technology and the need for enhanced communication strategies, (ii) nonharmonized and prescriptive regulatory requirements, and (iii) limited experience with regulations and product development within some public sector programs. The need for holistic resistance management programs to enable the most effective use of insect-protected crops was also a point of emphasis. This paper provides details on the symposium discussion and provides background information that can be used in support of further adoption of beneficial GM crops. Overall, it emphasizes that global adoption of modern agricultural biotechnology has not only provided benefits to growers and consumers but has great potential to provide solutions to an increasing global population and diminishing agricultural land. This potential will be realized by continued scientific innovation, harmonized regulatory systems, and broader communication of the benefits of the high-yielding, disease-resistant, and nutritionally enhanced crops attainable through modern biotechnology.

KEYWORDS: *agricultural biotechnology, genetically modified crops, regulatory assessments*

INTRODUCTION

Technical advances in biotechnology are driving the development of improved insect-protected, herbicide-tolerant, stress-tolerant, and nutritionally enhanced crops. Since their first commercialization in 1996, the cultivation area of genetically modified (GM) crops has increased every year, including 12 years of double-digit growth.[1] In 2014, GM crops were planted by a record 18 million farmers in 28 countries encompassing a total of 181.5 million hectares. However, despite convincing scientific evidence of the benefits[1,2] and safety[2,3] of GM crops, societal factors and well-funded opposition continue to foster resistance to modern agricultural technology.[4] For example, concerns over a potential consumer backlash in the United States has hindered the commercialization of a nutritionally beneficial potato;[5] even products with life-saving potential, such as Golden Rice, have faced opposition.[6]

Improved crop varieties are the cornerstone of agriculture.[7−11] To meet the challenges of population growth, diminishing high-quality agricultural production land, and rapid urbanization, the global agricultural sector is extensively

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using breeding tools afforded by modern biotechnology.[12,13] Over the past 80 years, improved crop varieties have accounted for half of all improvements in agricultural productivity with, for example, U.S. crop yields increasing by 2.5−4-fold for cotton, soybean, and wheat and an amazing 70-fold for maize.[10] A dramatic increase in wheat and rice yields, targeted for use in the developing world, was a central part of the "Green Revolution".[14]

Agricultural biotechnologies offer an unprecedented capability to greatly accelerate improvements in crops, especially for traits that are lacking in crop genomes. These traits include insect, herbicide, and disease resistance, salt and drought tolerance, and enhanced use of nitrogen as well as quality traits such as increased β-carotene. These traits can improve nutritional quality and reduce the need for agricultural inputs such as fertilizers, pesticides, and water, which is particularly useful for smallholder farmers who may not have easy access to these inputs. Importantly for global adoption and development work, GM crops are scale-neutral, with developing world farmers being the biggest adopters in terms of both number of farmers and land area.[1]

Recently, the 2014 IUPAC International Congress of Pesticide Chemistry (San Francisco, CA, USA; August 2014) included a symposium on "Challenges Associated with Global Adoption of Agricultural Biotechnology". Topics addressed by symposium presenters included (i) poor public understanding of GM technology and the need for enhanced communication strategies, (ii) nonharmonized and prescriptive regulatory requirements, and (iii) limited experience with regulations and product development within some public sector programs. The need for holistic resistance management programs to enable the most effective use of insect-protected crops and to address adaptive pests was also a point of emphasis. It was considered at the symposium that challenges to the adoption of modern agricultural biotechnology may disproportionately affect developing countries, as well as smaller entrepreneurial and public sector initiatives. This paper reviews the symposium discussion and provides background information that can be used to support further adoption of beneficial crops developed through modern agricultural biotechnology.

At the symposium, Huesing and Braverman showed that programs to enable adoption of GM crops globally and through public sector initiatives are already in place. In this paper, Huesing provides an overview of the U.S. Agency for International Development (USAID) "Feed the Future" program and its role in supporting the global development of agriculture sectors. Braverman describes the Interregional Research Project Number 4 (IR-4) Project, a pathway for public sector biotechnology registration in the United States that has been successfully leveraged by academic groups.

Subsequent sections of the paper highlight challenges in GM adoption. Shelton provides examples where GM cultivation has been suspended despite clear evidence of it success. Felsot highlights some of the misconceptions about GM technology that can provoke public concern as well as moratoriums of the type addressed by Shelton. Several symposium presenters (Andres, van Rijssen, and Burns) comment on the demands required by some regulatory systems and challenges in establishing regulatory expertise in developing countries. Finally, Hellmich and Reynolds stress the importance of developing effective, holistic insect resistance management programs that can enable broader cultivation of insect-protected (Bt) corn hybrids.

■ ENABLING GLOBAL ADOPTION

Three-fourths of the world's chronically poor and hungry live and farm in rural areas of developing countries, particularly in sub-Saharan Africa.[7,8] There is broad consensus that economic growth originating in the agricultural sector is one of the most effective routes for increasing incomes of the rural poor, yet <5% of development assistance and public spending targets agriculture in these countries.[8] "Feed the Future" is the U.S. government's hunger and food security initiative to address global hunger. Focused on smallholder farmers, particularly women, "Feed the Future" supports partner countries in developing their agriculture sectors to accelerate economic growth, increase incomes, and reduce hunger, poverty, and malnutrition. Led by the U.S. Agency for International Development (USAID), "Feed the Future" works with agencies across the U.S. government using a "whole of government" approach to partner with other governments, donor organizations, the private sector, and civil society to enable its long-term success.

USAID supports the development, release, and stewardship of improved GM crops at all stages of the product development pipeline. USAID has substantial involvement in providing oversight in all aspects of the regulatory approval and stewardship phases of projects in which it invests. USAID has statutory requirements to ensure that the environmental consequences of USAID-funded activities are identified and considered by USAID and the host country prior to a final decision to proceed and that appropriate environmental safeguards are adopted. Accordingly, USAID requires that all regulatory submissions related to GM crops developed with USAID funding comply with internationally accepted standards as exemplified by the *Codex Alimentarius* and U.S. regulatory agencies.

To support its goals, parallel investments in partner countries assist with building effective regulatory systems and ensuring that decision makers have the resources they need to make informed decisions about biosafety. In addition, extensive regulatory training and support of product developers ensures appropriate safety measures are taken while GM crops are moved through the regulatory process. To meet this latter challenge, USAID has recently refocused efforts to ensure that in-country capacity is developed to ensure quality regulatory data packages.

Multinational commercial seed companies are organized and resourced to successfully meet GM product development challenges.[15] In particular, they possess the necessary human resource skill sets to successfully orchestrate these complex regulatory operations. Conversely, public−private partnerships (PPP), which are largely driven by research institutions, are not generally organized or staffed with regulatory professionals. To address this issue, USAID works with development partners to identify expert consultants (primarily industry regulatory affairs retirees) who have extensive proven hands-on experience in developing and submitting regulatory dossiers for GM crops. These experts work hand-in-hand with in-country product developers to build the needed capacity and expertise in the regulatory sciences so that partner countries and institutions, primarily the National Agricultural Research Institutions (NARIs), will have the expertise to develop and submit strong regulatory dossiers that lead to commercialized crops targeted for the benefit of their low-resource farmers. This approach, comprising the development of host country governmental

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regulatory expertise combined with the development of regulatory affairs expertise in national research institutions, will provide developing partner countries with the capability to develop GM crops targeting their specific needs in a safe, transparent, and expeditious manner.

Regulatory approval of public sector biotechnology research meant for commercial release is still one the major barriers between research and availability of technologies to growers. Unfortunately, as pointed out by Braverman, most biotechnology research ends with only a journal publication due to a lack of resources, product development and regulatory experience, and professional reward for such efforts. Furthermore, the time and expenses involved are beyond the means of most researchers and are frequently outside the scope of their parent organization. For example, a large number of trait events have been developed by researchers but only a small number of petitions have been submitted and approved for deregulation, and very few of those have been in specialty or minor crops.[16,17] About a decade ago the Specialty Crops Regulatory Initiative[18] was formed to address this issue, but without funding and without any regulatory staff, they have not secured any registrations or even made a submission to the U.S. Environmental Protection Agency (EPA).

Since 1963, the Interregional Research Project Number 4 (IR-4) has developed data, primarily on residue studies of conventional chemistries, to obtain U.S. EPA pesticide registrations. IR-4 was formed due to the lack of financial incentive by major companies to develop pesticide registrations for specialty crops. In 1982, regulatory assistance was expanded to cover biopesticides because of the history of regulation of *Bacillus thuringiensis* (Bt) microbial pesticides and initial biotechnology efforts focusing on Bt Cry proteins. IR-4 had extensive experience with microbial pesticides; therefore, the extension to biotechnology registrations based on these same microbes, as well as to other traits, was natural. Similar to conventional chemicals, major manufacturers have focused on maize, cotton, and soybeans rather than fruits and vegetables, thus providing an area of focus for IR-4. Funded primarily through the National Institute of Food and Agriculture (NIFA),[19,20] the IR-4 Project is able to provide guidance, consultation, and submission of documents. IR-4 has successfully assisted in the U.S. EPA registration of Honeysweet Plum, a genetically engineered plum resistant to plum pox virus.[21] IR-4 also assisted in some of the initial phases of RNAi work on the Israeli Acute Paralysis Virus affecting bees. More recently, IR-4 has taken on additional projects on tomato, walnuts. and roses.

SCIENTIFIC MISUNDERSTANDING: CAUSES AND CONSEQUENCES

Shelton described how he and his colleagues who are trying to improve pest management have been frustrated to witness campaigns against GM crops. The often inaccurate information disseminated in such campaigns is galling to them because these pest management crops have undergone strict safety testing[15] and have dramatically reduced pesticide inputs.[2]

What are the roots of such campaigns? Sociologists would argue that cultural politics plays an important role in shaping our political, economic, and social values. Many who advocate against GM crops identify with anticorporate organic "natural" agriculture. This anticorporate sentiment is often expressed by those who claim to fear corporate control of the food system or believe that corporations will put profit ahead of corporate responsibility in society's most basic need.

Of direct relevance to global adoption, differences in the perceptions of the value of GM crops are evident between developing countries, where agriculture plays a prominent role in the daily lives of the majority of people, and industrialized countries, where only a small proportion, <2% in the United States, is involved in agricultural production. This is one of the reasons that the area grown to GM crops in developing countries now exceeds that grown in industrialized countries.[1] But even between industrialized countries that have high living standards there are differences in perceptions about GM crops. In *Cultural Politics and the Transatlantic Divide over GMOs* Stephan[22] suggests that Europeans, more so than Americans, connect agriculture to positive images of "nature". As such, they are more likely to associate agricultural biotechnology with broader and "troubling cultural and socio-economic changes" than are Americans, who are more likely, despite some opposition, to be more pragmatic. As observed later (Andres, Burns) cultural factors strongly influence the differences in regulatory frameworks adopted in Europe and in the United States.

Despite these cultural differences about GM crops and campaigns of disinformation to discredit them, their adoption rate globally continues to increase.[1] However, it should be pointed out that the presently commercialized GM crops have almost exclusively been industrialized crops including soybean, maize, cotton, and canola. The reason for this is largely due to the costs of developing and stewarding them. The adoption of GM vegetables and fruits has accordingly lagged in comparison. Except for small amounts of GM insect-resistant sweet corn and disease-resistant squash and papaya, there has been minimal development of GM technology for fresh food crops. This is unfortunate because 45% of the value of all insecticides is applied to fruits and vegetables,[23] an amount that greatly exceeds the combined insecticide use on maize, cotton, and rice.

Fruits and vegetables are food crops, so there is increased sensitivity about their production and continued misunderstanding about how GM technology can be used to benefit their production. Thus, they are susceptible to campaigns to limit their adoption, in both industrialized and developing countries. Two recent examples illustrate this point: GM papaya in Hawaii and GM eggplant in India, Bangladesh, and the Philippines.

GM papaya was introduced in 1998, saving the Hawaiian papaya industry from the devastating papaya ringspot virus (PRSV) disease. PRSV is spread by aphids that feed on infected papaya trees. Trying to control the aphid with insecticides is ineffective and environmentally damaging. Notably, GM papaya was developed by a native Hawaiian, and USDA Agricultural Research Service (ARS) scientist, without any profit to the developer or a corporation, by incorporating a fragment of the virus into the papaya genome to prevent virus replication.[24] The GM papaya was distributed free to farmers, most of whom are small-scale, multigeneration Filipino farmers, and now it is estimated that 85% of all the papaya grown in Hawaii is GM. However, in 2013 legislation was introduced to ban all GM crops, including papaya, on the Big Island of Hawaii. Shelton visited the Big Island in 2013 and found that this legislation was the result of a well-organized disinformation campaign. The inaccurate information about GM crops heard at the public hearings was widespread and voiced largely by outside interests.

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The result was a law that went into effect on March 3, 2014, to ban all GM crops, except GM papaya, on the Big Island. GM papaya was excluded from the ban because it had allegedly "contaminated" the island and "could not be removed because it was so widespread". The law, however, is being challenged, and its fate is uncertain.[25]

In India, Bangladesh, and the Philippines, a similar campaign was waged against commercialization of insect-resistant eggplant. Eggplant is a common vegetable in these countries and is attacked by a caterpillar known as the eggplant fruit and shoot borer. Farmers commonly spray insecticide several times a week to protect their crop. The insecticides used are broad-spectrum and applied by workers who may not wear personal protective equipment. The hazards to the workers, consumers, and the environment are well documented.[26,27] Beginning in early 2000s, efforts were initiated to develop insect-resistant eggplant by having it express a bacterial protein (Bt) similar to that in currently commercialized insect-resistant cotton and corn. After a decade of development and laboratory and field trials and passing all requirements by regulatory agencies, Bt eggplant was positioned to become the first GM food crop in India. However, because of a reported $100 million dollar campaign by a multinational non-governmental organization (NGO), the Minister of the Environment and Forests put a moratorium on its commercialization on February 9, 2010. A similar bank was upheld in the Philippines.[72]The result is that farmers in a developing country cannot access a safe, economically beneficial, and healthy product.[26,27]

In Bangladesh, the government approved Bt eggplant to be conditionally cultivated and sold on a commercial basis starting in 2014. Initially, Bt eggplant was grown in 20 farmer fields beginning in January with an additional 108 farms in 2015. Despite a campaign of opposition, farmers overall are supportive of Bt eggplant.[28] Today, proactive initiatives to highlight the value of modern agricultural biotechnology and science to enable solutions to food security and safety are appearing. An example is the Bill & Melinda Gates funded project, the Cornell Alliance for Science, whose goal is to help inform the debate about biotechnology in agriculture.

As pointed out by Felsot, public lack of familiarity with biotechnology and agriculture has arguably led to feelings of uncertainty about GM crops. Citizen initiatives in several American states and counties therein may be attempts to absolve this uncertainty by mandating the use of labels declaring a food genetically engineered and/or the outright banning of planting such crops.[29,30] These initiatives typically invoke some form of the precautionary principle (PP)[31] to reject GM crops based on a perceived absence of definitive proof of safety, a goal that scientifically is unattainable. As noted by Shelton above, the PP is often tied to identity politics best illustrated by the GM debate in the European Union (EU). Invoking the PP in EU policy, for example, has brought a near lockout of grower cultivation of GM crops in Europe, but interestingly, not a ban on import of such material for food and feed uses.[32] EU policy against cultivation of GM crops may be based on arguments that McHughen suggests are "marked with much ignorance and misinformation".[32] Felton described five misconceptions around GM technology that illustrate the inappropriate invocation of the PP to risk management of agricultural biotechnology.

Misconception 1: U.S. Policies for Regulating GM Crops Are Inferior to the PP-Driven Policies of the EU. In fact, the United States and EU[33] both require premarket risk assessment of GM crops with the only difference ultimately being the architecture of the statutory mandates. In the EU, the PP is invoked in policy directives as a philosophical imperative but is not explicitly defined. The U.S. regulatory system involves three regulatory agencies (USDA, FDA, and EPA) that operate under separate statutes but within a *Coordinated Framework for the Regulation of Biotechnology* under 51 FR 23302.[34] In the U.S. system precaution is an important policy component. For example, a permit from USDA is required prior to the field testing of new GM events. Only after a plant pest risk assessment and a formal environmental assessment, as required under the National Environmental Policy Act (NEPA), will USDA declare an event to have "non-regulated" status, which obviates the need for permitting and paves the way for commercialization. The U.S. EPA regulates crop traits classified as plant-incorporated protectants (PIPs) under the statutory mandates of FIFRA (Federal Insecticide Fungicide Rodenticide Act) (see Hellmich and Reynolds later). In addition, EU regulations for traceability and postmarket surveillance are analogous to FIFRA section 6(s)(2) rules on "adverse effects reporting".

Misconception 2: Gene Transfer Is Not Natural. Horizontal (or lateral) gene transfer is presently recognized as a naturally important phenomenon in biological evolution, especially among prokaryotes.[35] The phenomenon has been estimated to occur in 50−60% of bacterial and archaeal taxa and among 10% of eukaryotes.[36] Some at the symposium suggested that, accordingly, plant breeders have simply added this naturally occurring process to the plant breeder's toolbox. In other words, what genetic engineering offers to plant breeding is a very precise means of transferring useful genes to crops for traits that may simply not exist in the crop gene pool, for example, drought tolerance or insect resistance. Comparatively speaking, the highly precise nature of genetic engineering may be far more attractive for some traits than the much less precise method of, for example, mutation breeding, widely used for crops including those cultivated in organic agriculture.[37] Felsot further added that the fact that *Agrobacterium tumefaciens* can transfer a functional virulence gene to a host plant's genome is an ironic testament to a case for the "naturalness" of genetic engineering given that species' importance to genetic engineering. This can be now highlighted by the recent finding that sweet potato is a naturally transgenic food containing *Agrobacterium* T-DNAs with expressed genes.[38]

Misconception 3: GM Crops Do Not Yield Benefits. Independent studies show economic benefits to farms from yield increases while showing reductions in environmental impact.[39−41] Protestations of significant increases in pesticide use, especially of herbicides, based on singular analyses,[42] are refuted by other studies of pesticide use decreases or nonstatistically significant increases.[2,26,27] Studies have also documented decreases in worker poisonings from insecticides.[43] Overall, the data are very clear on the yield and safety benefits of GM crops to growers best illustrated by the level of adoption of these GM varieties in both the developing and developed worlds.[1]

Some presenters at the symposium further considered that the argument should not simply be around the issue of increases or decreases in the abundance of a particular compound in the environment per se. It should be around issues such as precision, safety, and efficacy. If, for example, an increase in a relatively safe herbicide results in a significant decrease in soil erosion or emission of climate-degrading gases,

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then the use of that compound, if safe for the intended use, should be an option of choice. Likewise, for an insecticidal GM trait the overall increase in environmental safety in terms of effects on nontarget organisms or ecosystem services has been very positive. Using that approach, it is clear that the use of many GM traits is more benign than other production options. In many cases, the use of harmful pesticides is replaced with safer pesticides, and their application is more precise, thereby increasing applicator and consumer safety.

Misconception 4: GM Product Labeling Provides Consumers with Choice. Globally, there are different approaches to GM product labeling.[44] The EU policy of requiring GMO labeling is held as an example of the PP and a moral principle of the "right to know". Products that intentionally use GM derivatives must be labeled in the EU, but labeling requirements are threshold-based (e.g., adventitious presence of 0.9% GM does not require labeling). Monitoring of various products containing soybeans or corn shows significant percentages of unlabeled food or feed containing GM biomarkers below country-established thresholds.[45−48] Conversely, products that contain ingredients derived from a GM source but that are not identifiable as GM by analysis require labeling in the EU as a means to provide evidence of GM traceability. Thus, GM labeling extends to highly refined products such as vegetable oil or sugar, in which the GM DNA or resulting protein is no longer present or detectable.

Misconception 5: PP-Based Management Fosters Democratization of Technology. The U.S. risk assessment framework and regulatory data requirements guide what studies are required for risk characterizations that inform risk management. The deregulation and approval process is costly, and many universities or other nonprofit entities are unable to fulfill the rgulatory burden necessary to commercialize new biotechnology-derived cultivars despite benefits for health, environmental resiliency, and energy production.[49,50] Thus, the rigor of the regulatory process has centralized crop breeding rather than democratized it.

If opposition to GM technology is indeed based in "ignorance and misinformation", how can the above misconceptions be dispelled? A key will be addressing public perceptions through improved communication and educational efforts in schools that emphasize modern biological subjects. For now, however, application of the PP has not increased environmental or health safety and has needlessly delayed the introduction of safe and useful crops: a goal of the educational effort should be to explain why a "precautionary approach" to regulation is a more practical approach than the poorly operationalized precautionary principle.

REGULATORY ISSUES

Earlier, Huesing observed that regulatory challenges extend to infrastructure and knowledge gaps in developing functioning biosafety programs in developing countries. As pointed out by Jansen van Rijssen, the creation of regulatory frameworks for adopting GM crops has been a slow process in Africa. South Africa, with established GMO legislation since 1997, has often been held as an example of good GMO governance and the entrance to GMO production in Africa. However, South Africa has limitations in approving GMO permits, and its experiences may provide important lessons for other developing countries.

The South African government has approved nine GM events for general release since 1997, and the technology owners are multinational companies. A number of events from national research and academic institutions were not approved. The reasons given, in a number of cases, were socio-economic and trade issues but also included environmental and food safety. The appeals by the applicants against government decisions resulted in increased permit conditions such as more stringent contained experimental requirements. In some cases research was discontinued or taken elsewhere. Investing in local research has become less attractive because of increased expenses and long delays. This situation directly or indirectly results in researchers resigning or turning to different avenues of research.

Because of this situation, the question arose: What was South Africa doing wrong? To seek an answer, Jansen van Rijssen and colleagues started by analyzing South African risk governance of GMOs. South African legislation resembles the *Codex Alimentarius* model of risk governance except for the most transparent phase of risk assessment policy development. The GMO Act of South Africa provides for a GMO Executive Council and an independent GMO Advisory Committee. The council members represent different relevant government departments, each with its own mandate; decisions require consensus agreement from the council members. Mandates of the government departments may have conflicting purposes; for example, food security may be more emphasized than environmental protection. In addition, each government department requires an individual assessment of the documentation by its regulatory scientists in addition to the reviews by the expert advisory committee. Role conflicts have not been resolved despite the noble intentions of the national biotechnology strategy in the past. However, a new bioeconomy strategy announced in 2014 may be more successful. The GMO advisory committee, in turn, consists of academics and independent scientists. These prestigious appointments, unfortunately, demand time-consuming dedication without adequate remuneration. Peer reviewing for risk assessment is an important requirement to ensure credibility, but has many challenges. The number of independent scientists (e.g., experts in environmental risk assessment, plant breeding, animal scientists, and toxicologists) that are qualified and willing to review applications for permits, that are specifically related to food safety and environmental safety, is limited. A shortage of toxicologists, a scarce skill, creates great concern, affecting sectors of agriculture, food/animal safety, environmental safety, and pharmaceuticals. The newly approved bioeconomy strategy of South Africa places an even greater demand on scarce skills.

The committee scientists do not have sufficient opportunities to gain international exposure to bodies such as the *Codex Alimentarius*, UNEP, and the Organization for Economic Cooperation and Development (OECD). These are mostly reserved for policy makers and government regulatory scientists, who are, in the case of South Africa, not considered as expert advisors. International exposure to particularly the approaches to risk assessment is, therefore, limited or almost nonexistent. Academics are constrained by a narrow focus on specialized fields of research, not directed at a risk assessment approach. Training in risk assessment is therefore of great importance. Unfortunately, funding of such interactions, internationally and nationally, remains problematic. In a study[51] conducted with a number of scientists familiar with the regulatory process, one of the main issues identified was improved communication between decision makers and

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stakeholders. Specifically, the legislated introduction of structured communication could contribute to a solution. Such an interface between the council members (decision makers), the committee, and stakeholders should be considered. The interface could foster scientific collaboration, provide for interaction with a number of additional scientists, provide policy development for improving regulatory training, and provide a foundation for scientific framing of reviews and other matters related to GM crop regulation of importance in a participative and transparent manner. This could be a step forward toward, in time, reducing delays and expediting the approval of new GM events.

There have also been many expressed concerns about regulatory systems in developed countries. The demonstrated safety of the GM process is reflected in the approach to regulation used by some agencies, for example, in Canada, but less so elsewhere. The Canadian regulatory approach is product-based and covers plants with a novel trait (PNT) sufficiently different from those of the same or similar species, regardless of the breeding method used in their development. PNTs include GM crops as well as some produced by more conventional breeding techniques. Other agencies have provided increasingly prescriptive and country-specific requirements. Andres commented on the European regulatory environment, which he considered to be highly politicized, and described some of the prescriptive requirements of the European Food Safety Authority (EFSA), which have provided a major challenge for GM developers. EFSA makes available guidelines that provide information on the risk assessments that must be submitted to support applications for approval for food and feed use and for cultivation in the EU of GM crops. Although these guidelines allow a case-by-case evaluation of each product, there are very prescriptive requirements regarding how the data must be generated and analyzed (e.g., following highly specific statistical approaches including both difference and equivalence testing), and they are not in line with other international regulatory frameworks. These requirements represent a major challenge for developers as any GM product entering the EU for food, feed, or processing must be approved and for that, regulatory packages must comply with these data requirements, but not only in terms of which data must be provided but also in terms of how the data must be generated. This prevents, in most cases, data transportability. Regulatory packages are constructed following the EU rules, thus adding considerable cost and resources without providing data that are more informative for risk assessments. This results in different regulatory packages for the EU and the rest of the world. Moreover, the European Commission has now made this guidance legally binding in implementing regulation. Together with the systematic voting of a number of Member States against EFSA opinions, Andres, representing EuropaBio (European Association for Bioindustries), considers that the EU has developed into one of the most convoluted and unpredictable regulatory frameworks for the authorization of GM crops in the world.

Challenges of onerous regulatory data generation were also addressed by Burns, who argued that the proven hypothesis-driven problem formulation approach used globally offered advantages over prescriptive data-gathering approaches. As she observed, GM crops undergo extensive testing prior to commercialization to test the hypothesis that their cultivation poses negligible risk to the environment. Testing is directed by problem formulation. Conceptual models are helpful tools for identifying testable risk hypotheses during problem formulation and can be tailored to the GM crop and its intended use. Risk hypotheses can then be tested by collecting information from the literature and/or by generating new data.

When conceptual models for potential effects to nontarget organisms are developed, both hazard and potential exposure should be considered. The mode of action of the novel protein(s) produced by the genetically modified crop can inform hazard. The natural presence of that class of protein in the environment can inform whether prior environmental exposure has occurred and the intended use of the crop, that is, cultivation or import for food and feed use, can inform exposure associated with the GM crop. If the novel protein's mode of action is not related to toxicity and if similar proteins are abundant in the environment and known to be of low hazard to nontarget organisms, then it can be concluded that the cultivation of a crop producing that novel protein poses negligible risk to nontarget organisms, including soil microbes.

In all cases, environmental exposure related to the import of grain for food and feed use is limited compared to exposure via cultivation. The only plausible scenario by which environmental exposure of genetically modified crop grain may occur is via accidental spillage, which can be mitigated by cleaning up spilled seeds. If seeds germinate, then environmental exposure to the crop is still likely to be spatially and temporally isolated. Therefore, a properly conducted environmental risk assessment (ERA) for cultivation of the GM crop also should satisfy the ERA for importation of the same crop product for food and feed use. In summary, problem formulation driven by science-based hypotheses is essential for developing a case-by-case approach to evaluate the safety of GM crops.

■ ENABLING INSECT MANAGEMENT PROGRAMS

The majority of GM crops have been developed as pest management tools, including the safe management of traditionally difficult to control insect pests. GM corn hybrids that target an important moth pest, the European corn borer, *Ostrinia nubilalis* Hübner, were first commercialized in 1996. These plants produce insecticidal crystalline (Cry) toxins, derived from *B. thuringiensis* (Bt). Bt corn has revolutionized how major corn insect pests are managed, but insect resistance management (IRM) strategies are essential for delaying pest resistance to the Cry toxins. Currently, preventive IRM is based on the high-dose/refuge (HDR) strategy[52,53] (Figure 1), which comprises three basic components: (i) resistance alleles must be rare and recessive; (ii) the Bt toxin must be delivered at a dose high enough to render heterozygotes functionally recessive, that is, kill 99.99% of susceptible insects; and (iii) a non-Bt corn refuge should be grown near Bt corn that produces an excess of homozygous susceptible individuals to mate at random with rare resistant individuals. This strategy appears to have been successful in delaying resistance to Cry1 Bt toxins in European corn borer,[54] and no evidence of field-evolved resistance has been detected after 18 years of Bt corn cultivation. The continued effectiveness and high adoption of Bt corn has led to a documented area-wide suppression of corn borer populations across the Corn Belt.[55]

In 2003, Bt corn hybrids were introduced that expressed the Cry3Bb1 toxin targeting the corn rootworm complex (*Diabrotica* spp.). The effectiveness of these hybrids led to rapid adoption by growers. However, currently available Cry3Bb1, Cry34/35Ab, and mCry3A Bt corn hybrids do not satisfy high-dose criteria.[56,57] In addition, resistance alleles in

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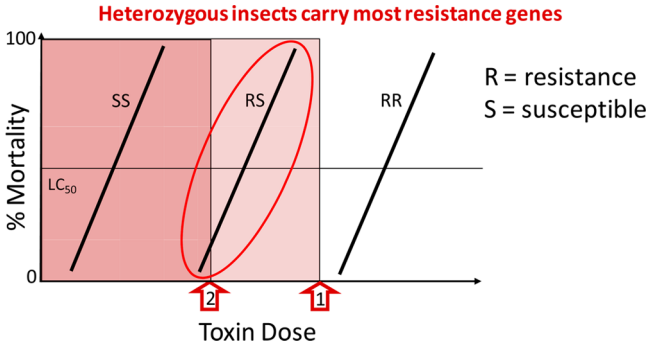

Figure 1. Dose mortality graph that demonstrates the importance of high-dose toxin in genetically engineered crops. With high dose (1) most if not all susceptible (SS) and heterozygous (RS) insects are killed; only the few resistant (RR) insects survive. However, with low dose or "not high dose" (2) many of heterozygous insects survive in addition to resistant insects. Resistance develops much more quickly with low-dose crops because most resistance genes (R) are carried by heterozygous insects.

western corn rootworm (WCR), *Diabrotica virgifera virgifera*, to Cry3Bb1 are probably less rare and incompletely recessive.[56−58] As a consequence, field resistance to Cry3Bb1 Bt corn evolved quickly and was confirmed in parts of Iowa less than seven years after its introduction.[59] Cry3Bb1-resistant WCR populations have now been documented in other states,[56,60] as well as populations cross-resistant to the modified Cry3A (mCry3A) Bt toxin.[61]

Resistance also has been documented among several lepidopteran species including the African stem borer, *Busseola fusca*, in South Africa,[62] and the fall armyworm, *Spodoptera frugiperda*, in Puerto Rico[63] and Brazil.[64] In all of these cases, toxin levels in Bt corn were not high-dose (Figure 1). These documented cases of field resistance have highlighted two major challenges to IRM relying on the HDR strategy: (i) Bt corn is not high dose for all target insects, and (ii) grower compliance for implementing the HDR strategy (i.e., planting and placement of refuges) in some regions is low.[65,66]

As part of its regulation of IRM for Bt crops, the U.S. EPA requires resistance monitoring for the major target pests of corn and cotton.[67] For corn rootworm (CRW) monitoring has consisted of two main components: (i) investigation of reports of unexpected field damage and (ii) monitoring for changes in susceptibility through targeted population sampling and testing. Unexpected damage reports may reveal the occurrence of localized resistance (or hot spots) before the effects become widespread. Targeted field sampling can reveal changes in susceptibility of geographically representative populations. In both cases, bioassays are used to determine the susceptibility of each sampled population. If resistance in sampled populations is confirmed in laboratory bioassays, a remedial action plan is triggered to mitigate the resistant population and ensure trait durability.

Resistance monitoring is conducted each year by Bt corn registrants and, for CRW, has been coordinated through the Agricultural Biotechnology Stewardship Technical Committee (ABSTC) with annual reports submitted to the U.S. EPA.[68]

CRW presents a number of challenges for resistance monitoring. The insect has one generation per year, undergoes obligate diapause, and feeds subterraneanly, factors that limit the ability to conduct susceptibility bioassays. CRW are also, as mentioned earlier, generally less sensitive to Bt toxins than other target pests of Bt corn (e.g., Lepidoptera). These factors can complicate both field scouting and interpretation of bioassays. Timing is also a concern; because of obligate diapause, a sampled population may not be tested (and determined to be resistant) until the following season.

Overall, in light of the challenges presented by CRW, the U.S. EPA has concluded that the current resistance monitoring program is reactive rather than proactive.[68] Shifts in susceptibility (prior to field failure) are not likely to be detected with current approaches. Rather, resistance will more likely be detected through the investigation of Bt field damage. Indeed, several researchers have reported detecting CRW resistant to Cry3Bb1 by testing populations collected from damaged fields with on-plant assays.[51,59,69] It should be noted these cases of resistance were not identified through the annual ABSTC monitoring efforts based on random population sampling and diet bioassays.

The U.S. EPA is concerned about the reports of CRW resistance to Bt corn, as resistance may increase the use of conventional insecticides and increase the vulnerability of more durable traits in pyramided products with a reduced refuge. In December 2013, the U.S. EPA convened a Science Advisory Panel (SAP) meeting to address scientific issues associated with CRW resistance monitoring and provide recommendations.[70] The U.S. EPA agrees with most of the panel recommendations and notes that industry has already implemented a number of these.[71] Input was also provided from other affected stakeholders including corn growers, grower associations, crop consultants, farm bureaus, crop protection industries, extension entomologists, and independent researchers via a public docket. The Agency plans to work with ABSTC to implement additional improvements for subsequent growing seasons.

Overall, the measures taken by the U.S. EPA will be important in informing improved steps to IRM, especially in global regions seeking access to Bt crops.

■ CONCLUDING REMARKS

Global adoption of GM crops has been slowed by many societal factors, many of which appear to be more pervasive in some geographic regions than in others. Factors discussed at the 2104 IUPAC symposium on "Challenges Associated with Global Adoption of Agricultural Biotechnology" included (i) poor public understanding of GM technology and the need for enhanced communication strategies, (ii) nonharmonized and prescriptive regulatory requirements, and (iii) limited experience with regulations and product development within some public sector programs. The need for holistic resistance management programs to enable the most effective use of insect-protected crops and to address adaptive pests was also a point of emphasis.

Despite the infrastructure and resources available to support the development of the agriculture sector globally, adoption of agricultural biotechnology still faces constraints. Many of these challenges can be attributed to complex regulatory systems but are generally symptomatic of a high level of misinformation and misconceptions surrounding modern agricultural biotechnology. Overall, however, it is clear that adoption of modern agricultural biotechnology has not only provided benefits to growers and consumers but has great potential to provide solutions to an increasing global population and diminishing agricultural land. It was a major conclusion of the symposium that this potential will be realized by continued scientific innovation, harmonized and practical regulatory systems, and

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broader communication of the benefits of the high-yielding, disease-resistant, and nutritionally enhanced crops attainable through modern biotechnology.

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Author Contributions

All authors participated in the drafting of this paper as individual subject matter experts in their fields, and the authors are solely responsible for the contents. Any views expressed in this paper are the views of the authors and do not necessarily represent the views of any organization, institution, or government with which they are affiliated or employed.

Notes

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