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Focus Issue: 50 years after Asilomar

Opinion

Risk-appropriate, science-based innovation regulations are important

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Inappropriate and often politicized regulations in many countries have limited the global benefits of agricultural biotechnology. The Cartagena Protocol on Biosafety (CPB) has proven to be one of the biggest barriers to biotechnological innovations, especially for food-insecure countries. The global movement of international agreements, such as the CPB, Convention on Biological Diversity, and Global Biodiversity Framework, contribute to the erosion of evidence-based regulation, enabling the development and spread of precaution-based regulatory frameworks. Despite 50 years of accumulated knowledge about the safety of genetic modification technology application since the Asilomar Conference, regulatory requirements are increasing, slowing innovation rates. This article discusses the importance of risk-appropriate regulation for innovation efficiency to avoid precaution-based regulation stifling innovation.

Highlights

The 1975 Asilomar Conference established risk-appropriate, evidence-based regulations for biotechnology.

The Cartagena Protocol on Biosafety is a risk-inappropriate, precaution-based regulatory framework that is a significant barrier to biotechnological innovation.

There is now a global scientific consensus on the safety of agricultural biotechnology products.

Major agricultural biotechnology–producing countries have not adopted the Cartagena Protocol on Biosafety.

The lack of agricultural biotechnology innovation adoption in some countries raises the risks of food insecurity.

Diffusion of the impact of the Asilomar Conference

The regulatory environment surrounding innovation in agricultural biotechnology is crucial to its development. Even before the first agricultural biotechnology (agbiotech) product was developed, a voluntary and self-imposed international moratorium on genetic modification research had been introduced by scientists who were beginning to create recombinant DNA (rDNA) [1]. The same scientists called for an international conference, now known as the **Asilomar Conference** (see Glossary), held in California in February 1975, and for a committee to develop safety guidelines and undertake further study into possible hazards to laboratory workers and the public from rDNA research. The first official US guidelines were issued by the National Institutes of Health (NIH) in July 1976. Similar guidelines were introduced by scientific academies around the world: Australia in 1975, Canada in 1977, and the UK in 1978 (Figure 1 provides a fuller timeline). Importantly, these guidelines have all seen many iterations since then: as the science and what we know about its risks has developed over the 50 years since the Asilomar Conference, so have the guidelines.

This perhaps is the key lesson from Asilomar – the value of accumulated knowledge and past experiences and the need to adjust as evidence changes. The science considered at Asilomar was innovative, and the nature and magnitude of its risks were unknown, but the risk tiers devised to regulate its use were built on evidence and knowledge gained from earlier work. Methods to protect worker safety and prevent escape to the environment were already in use in laboratories of the time, based in some cases on biosecurity standard operating procedures dealing with pathogens. The involvement of scientists in creating guidelines for rDNA meant that the guidelines were effective but also allowed (most) innovation to continue. But although evidence of the safety of genetic modification has grown to the point that most new research is not conducted in fully contained facilities, there has not been the expected rollback of its biosafety regulations to those comparable with their conventional breeding counterparts. Why not?

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The 50 years since Asilomar have seen governments increasingly rely on regulations to 'steer and direct society through its more complex economic and social challenges' [2]. In the agbiotech space, this is reflected in the inclusion of **socioeconomic considerations (SECs)** in the biosafety regulations used by some countries. Agbiotech regulation is no longer only about safety but also about broader issues, such as social and economic considerations and impacts. In parallel with the expansion of national and international regulation, there has also been a growing complexity of regulatory actors and influence of international networks of experts [2]. Regulatory decision-making has also become more politicized, with actors becoming more concerned about perception and approval of their constituencies than about evidence. The impacts of the **Convention on Biological Diversity (CBD)** and its protocols, particularly the **Cartagena Protocol on Biosafety (CPB)**, illustrate this in the regulation of agbiotech.

This growing complexity was predictable. At the time of the Asilomar Conference, genetic modification was possible only under strict containment conditions in the laboratory [3], and scientists creating the original guidelines made the decision to exclude objections on the basis of moral or ethical grounds [4]. Since Asilomar, genetic modification has moved in some research and development (R&D) systems from those implementing strict containment in the laboratory to those enabling the commercialization of beneficial products and knowledge in therapeutics, agriculture, food, and industry.

Society's response to risk itself has also changed. As well as broadening relevant considerations in biosafety regulation, some international and national agbiotech regulations have changed their approach to evidence assessment. The **Precautionary Principle** is the most significant change here – an interpretive principle taken from international environmental law that rejects lack of evidence of harm as a reason not to take precautions against harm.

Furthermore, one of the driving forces for the original guidelines was to establish self-regulation and avoid mandatory regulation by regulators [5]. Although the public of the past may have been satisfied that professional guidelines sufficiently addressed risk, many countries now use legally enforceable regulation for agbiotech and the sale of its products.

Two other fundamental changes impact Asilomar's legacy. The first is the public's (dis)satisfaction with the transparency and effectiveness of professional self-regulatory guidelines. Asilomar's success is often partly attributed to the inclusion of journalists at the conference to report to the public and that observance of the resulting guidelines was required for NIH grant funding [5]. But the 1975 meeting took place before social media, and society is now more fractured and difficult to engage with. Furthermore, even though observance of the guidelines that followed Asilomar was tied to grant funding, it was recognized at the time that the guidelines lacked relevance for researchers in private companies and others outside the public institutions.

The second fundamental change in biotech since Asilomar is in the research landscape itself. Many countries no longer support public research to the same extent as they did in 1975, making the already limited reach of guidelines tied to grant funding less effective. In any case, the development of multilateral intellectual property agreements and changes in domestic intellectual property laws, such as the 1980 passage of the US federal **Bayh-Dole Act**, enables universities, nonprofit institutions, and small businesses to own, patent, and commercialize inventions developed under federally funded research programs. This means those scientists now have the same imperative for greater caution in being transparent and in commercializing their work as those in the private sector.

Glossary

Asilomar Conference: this meeting was held in February 1975 in Asilomar, California, bringing together global leading scientific experts to share and discuss current knowledge regarding rDNA transfer experiments. It led to the development of rDNA experiment guidelines.
Bayh-Dole Act: American legislation allowing universities, nonprofit research institutions, and small businesses to own, patent, and commercialize inventions developed under federally funded research programs.
Cartagena Protocol on Biosafety (CPB): a subagreement of the Convention on Biological Diversity that was developed in 2000 and came into effect in 2003, focusing on the safe transboundary movement of living modified organisms.
Convention on Biological Diversity (CBD): negotiated in 1992 and ratified into effect in 1993, focusing on getting countries to commit to increasing sustainable development, the conservation of biodiversity, and the fair and equitable sharing of benefits arising from the use of genetic resources.
Global Biodiversity Framework (GBF): this framework was adopted by the parties to the CBD in 2022 and is focused on halting and reversing biodiversity loss by 30% by 2030, with further goals for 2050.
Precautionary Principle: originated in Europe in 1990 in regard to environmental damage to forestry and is a broad epistemological, philosophical, and legal approach to innovations with unknown potential for causing harm when extensive scientific knowledge on the matter is lacking. It emphasizes caution, pausing, and review before approving new technologies.
Socioeconomic considerations (SECs): are nonscience factors allowed within the auspices of the Cartagena Protocol on Biosafety that countries may choose to include as part of domestic biosafety regulations that may arise from the impact of living modified organisms on the conservation and sustainable use of biological diversity.

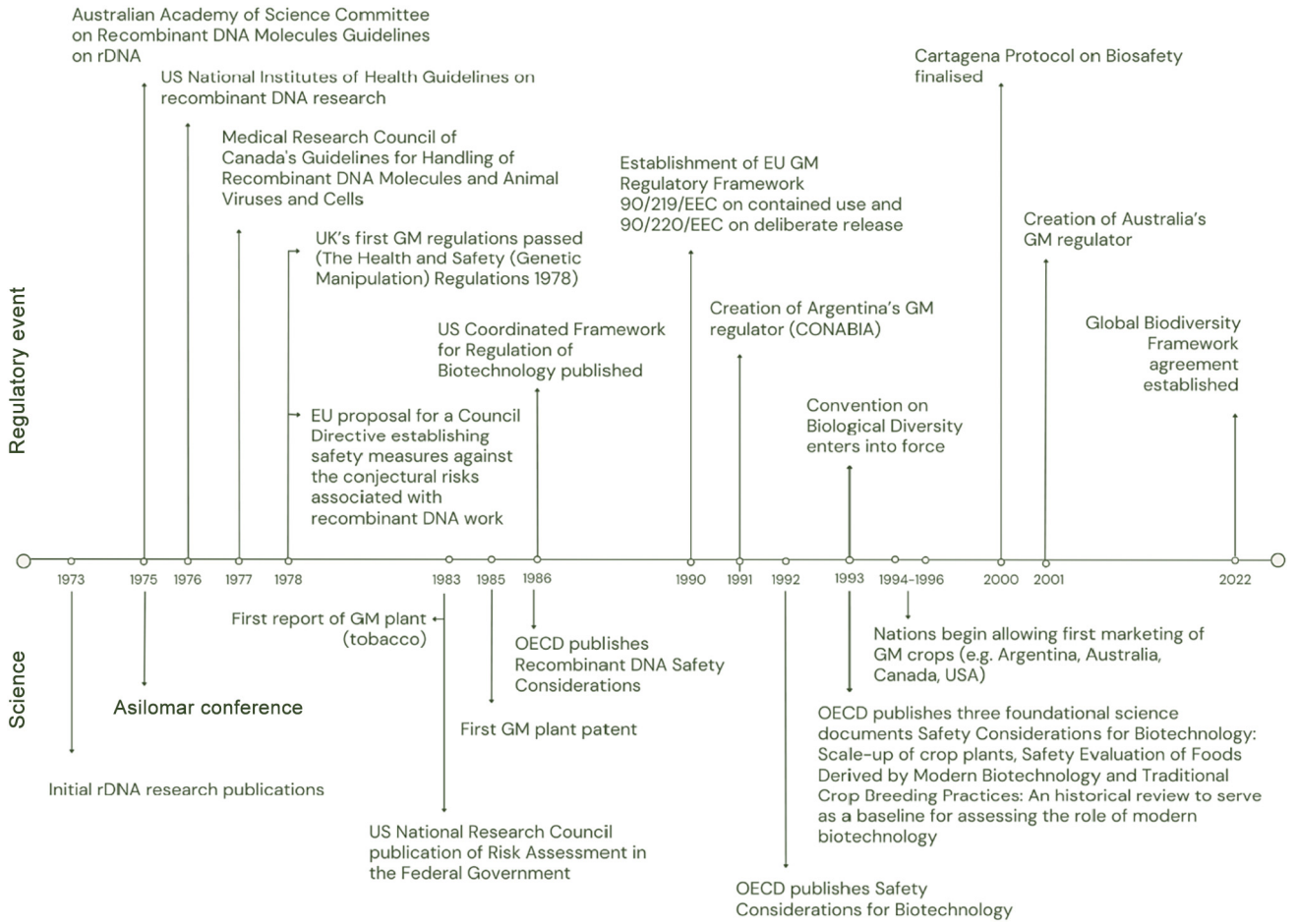

Figure 1. Timeline highlighting some of the key scientific innovations and regulatory document releases over the past 50 years. Abbreviations: GM, genetically modified; OECD, Organisation for Economic Cooperation and Development; rDNA, recombinant DNA.

Disagreement on preferred policy objectives and the role of evidence in regulation, a more risk-averse and skeptical public, and a more expensive research environment make consistent international regulation difficult. Since the 1992 establishment of the CBD, international environmentally focused agreements have become increasingly politicized and based on a strong interpretation of precautionary approaches in nature [6]. The architects of these agreements and moves by some members to export particular forms of biosafety regulation to CPB members via aid programs and the funding of national biosafety frameworks ignored the decades of robust evidence quantifying the safety of agbiotech products and processes.

International architecture transitions away from evidence

Asilomar and evidence-based regulations established the global regulatory framework for agbiotech from 1975 to 2000. As early agbiotech adopting countries developed domestic regulatory frameworks during the late 1980s and early 1990s, they were grounded in science, with the frameworks in Canada and the USA based on over 775 scientific publications, whereas the Organisation for Economic Cooperation and Development provided a further 400+ publications [7]. In the 1990s, even EU Member States were free to develop their own regulations regarding

commercial production, with field trials of genetically modified (GM) crops occurring in many EU countries. GM corn was successfully commercialized in Spain during this period, with Portugal following in 2005.

During the 1975–2000 period, evidence-based international agreements were the cornerstone of these global agreements. Witness the creation of the World Trade Organization (WTO) out of the previous General Agreement on Tariffs and Trade in 1995. The WTO established that scientific evidence would be required for any country to enact a trade barrier or tariff [8]. If robust scientific evidence was unable to support the barrier or tariff, it would be deemed illegal and the implementing country would be forced to remove it. As part of the support for science-based evidence, the negotiators of the WTO created the Dispute Settlement Mechanism (DSM), an evidence-based tribunal that determines the legitimacy of disputes regarding trade barriers [9]. In 2006, it was the DSM of the WTO that ruled the EU's moratorium on the import of GM products from 1999 to 2003, despite there being no scientific evidence to support the EU's position, was illegal because of undue delay in the approval process.

Post-2000, global agreements were developed and ratified that deliberately sought to move away from evidence-based regulation. The first instance of this was the 2000 agreement of the CPB, which came into force in 2003. The CPB is a subagreement of the CBD that came into force in 1993. The CPB was a radical departure from evidence-based regulation because it allows signatory countries to integrate SECs as part of their domestic biosafety regulations [10]. Although many negotiators hoped the CPB would enable the safe transfer of GM crops to developing countries, activist organizations focused their efforts on using the CPB to become a barrier to GM crop adoption. The inclusion of SEC considerations in biosafety regulations, as described in Article 26 of the CPB, is voluntary. This is by contrast to the other Articles in the CPB, which are mandatory. SEC factors that may be included as part of biosafety regulations include economic impacts on producers, consumer choice, ethics, traditional knowledge, and labor impacts, among others.

The effort to abandon previously deployed evidence-based regulatory approaches for GM crops is most evident in the realities of a complete lack of methodologies suitable for such assessment, robust or not, for many of the proposed SEC factors [10]. Parallel to the lack of methodology in many cases is the lack of data required to undertake a SEC assessment. Knowingly integrating SEC factors with no assessment methodology or data necessary to making an assessment highlights why the CPB is an agreement founded in unrealistic precaution, not science.

In 2022, the **Global Biodiversity Framework (GBF)** was agreed to, representing a further movement away from evidence-based regulation. The GBF provides 23 Targets relating to biodiversity protection and restoration (https://www.cbd.int/doc/decisions/cop-15/cop-15-dec-04-en.pdf). Several of these have particular importance for biotechnology. Target 7 calls for a 50% reduction in pesticide impacts, Target 10 calls for increased agroecology production, and Target 17 calls for strengthened biotechnology regulations. As part of the dialogue pertaining to the GBF Target 17, the CBD website states, 'New biotechnological developments are providing ever more promising opportunities, however the concerns over these technologies and the living modified organisms resulting from them are also increasing' (https://www.cbd.int/gbf/targets/17). Public 'concerns' vary from legitimate questions arising from lack of knowledge and information to unsubstantiated and negative perceptions held by activist organizations opposed to biological technologies, especially in agriculture. These are reflected in many cases in publications written by activist academics and organizations, often not published in peer-reviewed journals, which raise unsubstantiated concerns. Within the robust, peer-reviewed

literature, which spans over 25 years and over 1000 articles (Box 1), there is almost nothing to support claims about an increase in 'concerns' about agbiotech compared with conventional crops. Indeed, over 4400 risk assessments have been conducted by expert scientists in the 29 GM crop–producing countries and the 69 GM crop–importing countries since 1994 [11]. Every credible risk assessment has provided evidence and concluded that the risks of GM crop production do not differ from the risks of non–GM crop production.

Cartagena Protocol on Biosafety interaction with innovation

The Cartagena Protocol on Biosafety entered into force in 2003. As of 2024, the CPB has 173 parties, of which 170 are United Nations Member States. Over time, many countries have chosen to become parties to the CPB through different mechanisms, whereas others have not. Furthermore, some countries have chosen to adopt or not to adopt GM crop technologies, giving rise to the matrix shown in Table 1. Table 1 summarizes GM adopter status with CPB membership as a party as of 2019, the most recent date up to which public data on adoption are available. The complete data on the 55 CPB parties and adopter country combinations are given in Table S1 in the supplemental information online. CPB membership as a party requires the relevant country to comply with the CPB. As can be seen in Table 1, CPB membership as a party is associated more strongly with nonadoption of GM crops, with 30 of the 49 parties to the CPB not adopting GM crops, likely because of regulatory issues. Indeed, Table 1 may understate this association because it (and Table S1 in the supplemental information online) does not include the other 121 CPB parties that are not adopting GM crops for different reasons, including poor or insufficient R&D, human and financial resources, and regulatory and governance capacities. Certainly, a nonfunctional regulatory system does not help in this situation, although, as mentioned elsewhere in this article, the governance and adoption landscape is changing.

Box 1. Evidence of GM crop safety

Commercial production of GM crops began with canola, corn, cotton, and soy between 1995 and 1997 in Argentina, Canada, and the USA. By 1999, the first articles were published on the adoption impacts from GM crops [38,39]. Over the subsequent 25 years, the analysis of farm-level impacts of GM crop adoption have continued to increase, focusing on virtually all GM crop technologies in all adopting countries.

Temporal studies have been undertaken, further confirming that the initial risk assessments of GM crops were scientifically robust. In 2001, the EU released a report on 15 years of previous biotech studies involving 81 projects [40]. In 2010, the EU undertook an assessment of the 50 GM research projects funded during 2001–2010 [41]. Combined, these assessments reviewed 131 projects, involving over 500 different research groups and laboratories and over €500 million in funding. The conclusion of both reports is that GM technology is no riskier than conventional plant-breeding technologies. This 25-year period of assessment review found no robust scientific evidence of increased risk from the commercial production and consumption of GM crops.

In 2016, the American National Academies of Sciences, Engineering, and Medicine (NASEM) convened a panel to assess GM crops following 20 years of commercial production. The panel assessed over 900 scientific publications, concluding that there was no credible evidence to support claims that GM crops and foods are less safe than non-GM crops and foods [15]. The evidence that was examined supported conclusions that GM crops contribute to higher economic outcomes for adopters and reduced use of chemical inputs. Nevertheless, the NASEM report did recommend that regulations need to adapt with newer genetically engineered technologies and to continue monitoring for some unexpected environmental impacts, although these may not be significantly different from conventional crops.

With the NASEM report assessing over 900 articles, there are now well in excess of 1000 peer-reviewed publications on agbiotech. Complementing this literature are the 4485 risk assessments undertaken by all countries that produce and import GM crops [11]. Regulatory risk assessments began in 1994, and the 4485 assessments are until the end of 2019, with the current total in excess of 5000. From a scientific perspective, the risk assessments and literature provide conclusive evidence that GM crops and foods do not have a different risk profile from conventional crops, provide economic benefits to adopters, and reduce chemical inputs.

Table 1. Summary of member countries to the CPB and GM country adopter counts to 2019

		Adopter		
		Yes	No	Total
Party to the CPB	Yes	19	30	49
	No	5	1	6
	Total	24	31	55

This is not a proof of causality, because there are 19 CPB parties that have adopted GM crops. This shows that some countries have learned to navigate the requirements of the CPB against the pressing need for innovation to deal with their food security and climate change challenge needs. In essence, what these data show is the need to examine the enabling environment and the regulatory and governance pathways that lead to a functional biosafety system.

Three of the top five GM crop–producing countries have not ratified the CPB. The USA, Argentina, and Canada have all declined to ratify the CPB and are the first, third, and fourth largest producers of GM crops, respectively [11]. Conversely, Portugal and Spain remain the only countries within the EU to produce GM crops, with no additional EU countries permanently adopting GM crops in the past 25 years. Although only Portugal and Spain consistently produce GM corn, small amounts of GM corn and soybeans were previously grown in France, Germany, Sweden, Poland, the Czech Republic, Slovakia, and Romania. Europe's precaution-based regulatory preference has incurred a significant, negative economic impact. For example, in 1995, one-third of global agricultural R&D investments were made within the EU (https://croplifeeurope.eu/rd-trends-for-chemical-crop-protection-products/). By 2014, R&D investments in the EU accounted for less than 8%.

Evidence that precautionary regulatory approach slowed innovation

All formal regulatory processes are precautionary by definition. The existence of a governance structure involving a risk assessment and a decision-making process precludes an automatic approval of GM crops anywhere. The question from the standpoint of public policy analysis is how precautionary a system is in practice and the impact on innovation. Defining how precautionary a process is, is tied to the risk standard used for decision-making, the concepts of familiarity and knowledge status at the decision point, and risk proportionality.

The appetite for risk varies. In the strictest precautionary system possible, the risk threshold would imply 0% risk. This is clearly an impossibility. In turn, decision-making processes are typically based on the concepts of familiarity and knowledge about the crop, trait, and technology and the release environment. In principle, the greater the familiarity and knowledge about these characteristics, the less the need for additional regulatory scrutiny. This is the regulatory design concept of risk proportionality, where regulatory system efforts should be proportional to the risk level at hand.

Several literature reviews and meta-analyses have discussed the economic impact of evidence derived from GM crop technologies adoption [12–17]. The evidence tends to show variable but positive benefits to society from the crop and trait combinations studied. The evidence on estimating the trade-offs between innovation and regulatory approaches is thinner. Nevertheless, one can draw some lessons from such literature.

The innovation and risk literature has documented an overall a trade-off between innovation and precautionary regulatory approaches [18,19]. However, some innovations were possible

because some risk was incurred [20]. Although the cost of regulatory approvals needs to be carefully interpreted because of many estimation issues, signaling the need to contextualize such estimates [21], we can examine the literature assessing the trade-offs between regulatory approval processes, costs, and innovation.

Biden and colleagues [22] documented the potential losses from regulatory approval delays for canola in Australia. These include significant economic, environmental, and resource losses due to delays in the adoption of a GM canola in the order of AUS$485 million, 6.5 million kg of additional active ingredients applied, and 24.2 million kg of greenhouse gas and compound emissions released.

Raybould and Poppy [23] highlighted the cost of regulatory delays in terms of opportunity lost to farmers in the EU. These losses include higher commodity prices due to delays in importation permits, loss of opportunity benefits to farmers, increased application of productive inputs, and pest control ingredients. Similar outcomes have been described by Nang'ayo and colleagues [24] for the situation in sub-Saharan Africa, and Xiao and Kerr [25] documented the impact of regulatory delays in China, whereas Kumar and colleagues [26] summarized the importance of innovation of regulatory processes in developing countries. Kalaitzandonakes and colleagues [27] estimated potential losses due to GM crop regulatory delays impact on trade.

These outcomes are not exclusive to plants. Van Eenennaam and colleagues [28] documented similar outcomes in the livestock sector. These authors documented a 10-year delay beyond the expected and standard 10-year time frame for the evaluation of GM animal projects. The results are billions of dollars in lost opportunity benefits and reduced global food security. It is important to note that the examined literature has been related to GM applications. The situation may be different for gene/genome-edited applications. For example, Whelan and colleagues [29] documented a different regulatory pathway for gene-edited products in Argentina in terms of reduced timelines and cost.

In summary, experience with GM crops has shown that regulatory approaches that are unnecessarily precautionary can have real impacts on innovation and thus on products in the hands of users [15]. Decisions taken by a particular country can go beyond its jurisdiction, affecting other countries' decisions [30]. These decisions may reflect an unbalanced focus on risk without considering technology benefits, coupled with unrealistic burdens of proof of risk, such as those that require zero risk [31,32]. The outcome of this state of affairs is delays in technology benefit capture [33]. This outcome particularly affects the public sector and small and medium enterprises that typically face significant challenges to meet expensive, uncertain, and/or inefficient governance processes [34–36].

Concluding remarks

For the full potential of scientific innovations to be realized by society, efficient regulation is crucial. This is especially the case if science is to make meaningful contributions to achieving the United Nations' Sustainable Development Goals or the Paris Accord greenhouse gas emission reductions. It defies common sense to invest public research money in the development of new products and technologies to then only achieve one-third of their potential, as has been the case with GM crops [37]. This marginal level of benefit clearly illustrates an important repercussion of the global regulatory failure of agbiotech regulation (see Outstanding questions).

Efficient regulations rely on empirically based risk assessment methodologies and robust data to undertake risk-appropriate assessment of innovative products and technologies. Parallel to this is

Outstanding questions

By failing to adopt leading safe food production methods, how much yield has been globally sacrificed?

Can the precaution-based regulation trend be reversed and reintegrated with evidence-based regulation?

For countries wishing to improve domestic food security through evidence-based regulation, what method should be used to cease being a party to the Cartagena Protocol on Biosafety?

a variety approval decision-making process that makes decisions on the basis of scientific risk assessment and that has not become a politicized process that often functions as a mechanism to ban and/or delay all innovative and seemingly deemed safe GM products, regardless of their value to society. Some countries have implemented evidence-based risk assessment regulatory frameworks but have politicized variety approval processes that have banned the commercial production of GM crops for over 20 years.

More important, in the context of food insecurity, countries that grapple with food insecurity are increasingly turning to agbiotech as a contributor to resolving their food insecurity and climate change challenges. Such countries have taken a pragmatic approach where, even though they are CPB parties and thus mandated to comply with its requirements, they have developed and deployed pragmatic approaches including feasible and functional biosafety systems.

GM cowpea was commercialized in Nigeria in 2019 and has recently been approved in Ghana. In 2022, Kenya lifted its 10-year ban on the production of GM crops, facilitating the commercialization of GM corn. Numerous other countries that had previously expressed opposition to GM crop technology are making public announcements reversing previous policies and removing barriers regarding GM crop adoption. Honduras, a country with limited R&D capacities and a CPB party, developed and implemented a functional biosafety regulatory system that allowed crop and trait technologies valuable to the country to proceed after the proper biosafety evaluations. However, as discussed in the preceding text, inappropriate regulation will slow the achievement of benefits from GM crop adoption. Such countries will need to find a regulatory approach that enables the knowledge and experience gained since Asilomar to better facilitate innovation adoption.

With many international climate and environment agreements having 2030 as a target achievement date, there is a significant potential that many targets will not be reached, in large part because of inappropriate regulations. A fundamental underlying premise of science is that it builds on previous knowledge and experience. However, as many precautionary-based regulatory systems demonstrate, in many jurisdictions, virtually no lessons have been taken from the knowledge or experience gained since the development of the first rDNA guidelines 50 years ago. For innovation to reach its full potential, the knowledge of 50 years of safe agbiotech research and commercialization needs to be recognized and respected. Failure to do so risks unnecessary food insecurity and poverty.

Declaration of interests

The authors have no interests to declare.

Supplemental information

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