Challenges of Global Technology Assessment in Biotechnology—Bringing Clarity and Better Understanding in Fragmented Global Governance

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1 Introduction

Biotechnology deals with a matter that is fundamental to each person on earth: life itself. Worldwide, there may be different views on how we deal with different forms of life, and to what extent we, as human kind, are at liberty to alter and use animals, plants and other organisms for our own benefit. However, the (possible) impacts of developments in biotechnology touch on fundamental and universally-shared concerns such as our (shared) genetic heritage, illness and health, the safety and availability of food, and even the continued existence of our planet. In the current globalized world, a French scientist and an American scientist jointly won the Nobel prize (Ledford & Callaway, 2020) for a discovery that was used by a Chinese scientist to modify the genome of two embryos that grew into babies (Greely, 2019); a virus that originated in China has been able to bring nations worldwide to a halt, and (GM) crops, livestock products and food are distributed and eaten across the globe (MacDonald, 2015). Biotechnology therefore requires reflection on a global scale as well as international standards, agreements, and regulations.

Biotechnology involves the use and manipulation of living organisms such as plants, animals, humans, and biological systems, or parts of these, to modify their

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characteristics in order to create desired organisms or products. Traditional forms of such processes, such as brewing, baking, and fermenting with selected microorganisms, or breeding of animals and plants, have been utilized by humans for centuries, and are referred to as "old" biotechnology. In the 1970s, new methods to directly manipulate genes were developed. This field of genetic engineering forms the basis of "new" biotechnology, opening up a large amount of possible new applications in the fields of medicine, agriculture, and industry. But, it also raises a vast array of concerns, such as environmental and (human) health risks, moral objections to tampering with nature, and possible wider societal impacts. As such, new biotechnology has led to both public and political concerns.

This chapter investigates how technology assessment (TA) can contribute to a global approach to dealing with global issues concerning the use of biotechnology. Biotechnology development touches on many aspects that are central to TA. Concerns about the impact of engineered organisms on the environment, ethical issues regarding the relationships between humans and nature, and contributions to economic growth and broad prosperity are all factors that affect the societal acceptability of biotechnology. These factors clearly highlight a need for governance and legislation, since the interests of all stakeholders need to be taken into account. From the first breakthroughs in the 1970s, several activities have been undertaken to debate biotechnology developments and establish instruments for their governance. Examples of TA activities are stakeholder consultations evaluating the environmental risks of engineered organisms, analysis of the economic opportunities of biotechnology products, and ethical assessment of the modification of the genome of future generations. Similarly, instruments for the governance of biotechnology have taken shape on a global scale in different forms, for example regulating the trade of biotechnology products through trade agreements,[1] or fixing values in human rights treaties regarding the human genome.[2] However, developing governance structures on a global scale is challenging, because of regional cultural and social differences (Ladikas et al., 2015), and because there is no global authority that can adopt and enforce binding rules at the global level (Marchant, 2021).

In this chapter, we examine what institutions and types of regulations organize global governance on these matters; what (available) TA studies, insights and methodologies have contributed to global reflection, deliberation and governance; and what the challenges, requirements and opportunities for global TA are when dealing with issues concerning biotechnology. Section 2 gives a general introduction to international developments and governance responses concerning biotechnology since the 1970s. In Sect. 3, we discuss the global debate and activities in the field of TA on three key topics in biotechnology: genetically modified (GM) food and crops, synthetic biology, and human genome germline editing (HGGE). In Sect. 4, we discuss public perceptions, representing the cultural differences and perspectives

[1] E.g. the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the *Cartagena Protocol on Biosafety,* see Sects. 2 and 3 of this chapter.

[2] E.g. the UNESCO Universal Declaration on the Human Genome and Human Rights, see Sect. 3 of this chapter.

that need to be taken into account when trying to find ways toward global governance of biotechnology. In the final section, we reflect on the way ahead for global TA of biotechnology.

2 Early Developments in Biotechnology and Its Governance

An important breakthrough for modern biotechnology was the development of recombinant DNA technologies in the 1970s, with which DNA can be implanted (via a virus) into the genome of a bacterium (Jackson et al., 1972). From the beginning, it was evident that this was a controversial technology, encompassing both great potential benefits and risks. Therefore, activities to investigate and debate the consequences of biotechnology, and the possible actions that can be taken to mitigate the potential risks while stimulating the potential benefits were soon initiated.

A well-known example of this was what later came to be known as the *Asilomar Conference.* Biochemist Paul Berg, together with other scientists, initiated a voluntary moratorium on performing experiments with recombinant DNA technologies, awaiting an international conference regarding the biohazards of such experiments (Berg, 2008). At the 1975 International Congress on Recombinant DNA Molecules, at the Asilomar Conference Center in California, 140 biologists, lawyers, physicists, journalists, and government officials discussed the conditions under which experiments could safely continue. The recommendations formulated at the conference outlined the types of containment in the laboratory for different types of experiments. These recommendations formed the basis for the US National Institutes of Health (NIH) guidelines that were established in 1976. According to organizer Paul Berg, the Asilomar Conference is a good example of gaining the public's trust in science by taking their concerns seriously, and openly discussing the risks and the considerations that led to the resulting consensus. However, the Asilomar Conference is also criticized for adopting a narrow view of "risk", omitting other implications, such as social, political, and economic factors (Hurlbut et al., 2015). Similarly, a narrow range of viewpoints was included, as most participants were biologists from the US, with a few from Europe and none from the developing world, and no experts from other fields (i.e. social sciences) were included. Another criticism is that the conference focused overly on worst-case scenarios, setting a precedent for other debates about biotechnology and having a negative effect on public trust (Briggle, 2005). Thus, in hindsight the Asilomar Conference was perhaps not the best approach to discuss risk and uncertainty in science, technology and innovation.

Since the days of the Asimolar Conference, much better methods to take into account (often uncertain) impacts on both the environment and society of innovation, including genetic engineering, have been established in the related fields of Responsible Research and Innovation (RRI) and Technology Assessment. RRI is distinctive from TA by adding explicit ethical reflection (Grunwald, 2011). It has its origins in the need to address concerns with the emerging field of nanotechnology in the 2000s, in order to avoid negative impacts and to prevent the lack of acceptance

and active resistance by the public, as was the case with biotechnology (Rip, 2014). Moreover, as a response to the developments in biotechnology, many approaches to TA that emphasize public participation were developed (Einsiedel, 2012).

The first practical and commercial applications of biotechnologies emerged in the 1980s, together with the first regulations. For example, the first firms exploiting recombinant DNA technology were founded, the US Supreme Court ruled that recombinant micro-organisms can be patented under existing law, and a technique for recombination of DNA was patented. The judgment in Chakrabarty versus Diamond (1980) in the US paved the way for this, and resulted in rewriting the law in patenting of products of nature. This enabled the then nascent biotechnology industry to use intellectual property rights as a strategic tool for growth and attracting investments.[3] In 1982, the production of synthetic human insulin in a genetically modified bacterium (*E. coli*) was approved by the US Food and Drug Administration (FDA). As the commercial and international aspects of biotechnology became evident, TA activities that also include these aspects were initiated. In the US, the Office of Technology Assessment (OTA) published the report "Commercial Biotechnology: An International Analysis" (OTA, 1984), and a series of five reports on "New Developments in Biotechnology" in the late 1980s.[4]

In the 1980s and 1990s, the possible risks and benefits of biotechnology on a global scale were addressed by institutions such as the Organization for Economic Co-operation and Development (OECD), the Food and Agricultural Organization of the United Nations (FAO), the World Health Organization (WHO), and the World Trade Organization (WTO). Attempts were made to deal with global issues related to biotechnology, i.e., to set up structures for the governance of biotechnology through international consensus, coordination, and agreements. The OECD issued a report on international trends and perspectives on biotechnology in 1982, addressing the potential hazards of releasing genetically modified organisms into the environment (Bull et al., 1982). It also addressed the relationships between academic institutions and industry, and between fundamental and practical knowledge, with regards to biotechnology. The report also mentions the need for international discussion and coordination concerning the patenting of life-based products and safety issues in order to avoid differences in legislation and practice between countries. The OECD has since addressed issues related to biotechnology regularly. In 1993, the OECD established the Internal Co-ordination Group for Biotechnology (ICGB) to coordinate the impacts of biotechnology on different sectors such as: agriculture and trade; environment; science, technology and industry, bringing together different working groups, working parties, committees and fora that have activities related to biotechnology (OECD, 2021).

[3] See: https://cip2.gmu.edu/2021/01/29/forty-years-since-diamond-v-chakrabarty-legal-underpinnings-and-its-impact-on-the-biotechnology-industry-and-society/ (accessed 8-4-2022).

[4] On (1) the Ownership of Human Tissues and Cells (1987); (2) Public Perceptions of Biotechnology (1987); (3) Field-Testing Engineered Organisms: Genetic and Ecological Issues (1988); (4) U.S. Investment in Biotechnology (1988); and (5) Patenting Life (1989). See: https://ota.fas.org/otareports/topic/btopics/ (accessed 8-4-2022).

In 1991, the FAO and WHO released a joint consultation report on the safety of food produced by biotechnology, which was meant as a first step toward international consensus and providing guidance for the safety assessment of foods obtained using biotechnologies (FAO & WHO, 1982). In 1994, the WTO attempted to facilitate global trade by bridging the differences in Intellectual Property (IP) rights among its members and setting global standards, with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). According to the TRIPS agreement, the requirements for patentability, i.e., novelty, inventiveness and industrial utility, apply to biotechnology inventions as well. Hence, if new biological material is obtained through non-biological processes (such as genetic engineering), it is patentable. Member states do have the freedom to exclude plants, animals, and "essentially biological processes" from patentability.[5]

Biotechnology has been a central topic in the (institutionalized/parliamentary) TA community since the first OTA reports in the 1980s. From early on, an important question has been how to balance precaution with obtaining the possible benefits of biotechnology through regulation (POST, 1994; Torgersen & Bogner, 2004). This has been an ongoing discussion, as new developments in the field reveal gaps in the existing rules and regulations (see for example Habets et al., 2019 on the regulation of genome editing of plants and crops using novel gene editing technologies in the EU).

3 Key Topics in Biotechnology

In this section, we introduce three key topics in biotechnology: (i) genetically modified (GM) foods and crops, (ii) synthetic biology, and (iii) human genome germline editing (HGGE). Although these three topics do not cover all existing developments in biotechnology (i.e., pharmaceuticals, industrial biotechnology, genetic information, and privacy, etc.), together they cover many issues that are relevant for global governance of biotechnology in general. GM foods touch upon global trade and innovative competitiveness that can be in conflict with regional rules and values. It foregrounds issues such as food security, consumer rights to information, and transparent food labeling. The emergence of synthetic biology foregrounds issues of dual use and biosecurity. HGGE is considered to require a global approach as the human genome is often seen as matter that concerns all of humanity (i.e., a "heritage of humanity" in the words of UNESCO).

[5] See: https://www.wto.org/english/docs_e/legal_e/27-trips_04c_e.htm (accessed 8-4-2022).

3.1 Genetically Modified Foods and Crops

GM foods and crops are presented as a possible solution to hunger by organizations such as the United Nations (UN, 2021) and the WHO (WHO, 2021), as genetic engineering might increase crop yields, resistance against insects and disease, and nutritional values. The advantage of genetic engineering over traditional methods to breed new varieties of crops is that genes that code directly for a desired trait can directly be transferred from one variety to another. This makes it a faster and more accurate method. Moreover, the transfer of genes from one species to another is also possible. Hence, traits that naturally do not appear in a certain species can be introduced.

But, it has also led to fierce opposition by NGOs, for example by Greenpeace, which is internationally lobbying against GMOs because of the unknown risks and their unforeseeable environmental, social and health impacts (Greenpeace, 2021). One of the major concerns is that the novel gene might be transferred to other plants, such as wild relatives of the crop species, leading to the development of resistant "super weeds" and the destabilization of ecosystems. Other concerns relate to risks for human health, for example, when novel genes that originate from species that are usually not eaten by humans or animals are introduced to food crops. The concern is that this might lead to the introduction of unknown allergens into the food chain. Other objections to GM crops include tampering with nature, the monopolization of agrochemical and plant breeding companies, and negative consequences of introducing GM crops to agriculture, such as upscaling and a high use of pesticides and herbicides. In addition, freedom of choice for consumers and trade issues are considered to be important issues (Habets et al., 2019). The system of IP and patenting can lead to monopolization of GM seed producers and push prices up. If, as a result, only rich and large companies are able to afford the more expensive GM seeds, then the cultivation of GM crops will largely be in the hands of large companies, and small farmers might not be able to benefit from increased yields of GM crops. The humanitarian argument that GM food technologies might help to feed hungry people is thus contested by the concern that the benefits might not be equally distributed.

The global debate and governance of GM food

As food is traded across the globe, the governance of GM food and crops on a global scale mostly applies to trade-related agreements. The TRIPS agreement (1994) has helped globalization of biotechnology as it expanded the scope for patenting, and the leeway to exclude from patentability was limited. This could make investing in the development of GMOs more profitable. Under Article 27.3(b) patents on plant varieties was made possible, and although "essentially biological processes" could be excluded from patenting, patenting of plant varieties opened up the scope for patents on GMOs, and processes related to developing GMOs; as patents can also cover seeds, it ensured that plant variety protection was available for GM crops. The TRIPS Agreement, while providing flexibility to countries on granting IP rights over plant varieties, ensured that at least some form of protection should be granted. By

expanding the scope of IP rights on plant varieties, it also transformed the IP rights scenario related to seeds.

This flexibility left countries with limited choices, as they had to grant at least some form of IP protection rather than exempting plants and seeds, as was possible before. Because biotechnology was increasingly used to develop new plant varieties with new traits, IP protection was increasingly sought and granted on DNA fragments, genetically modified gene parts, and genetically modified organisms including plants. This expansion helped large companies like Monsanto to capitalize on IP protection and to consolidate their position in the global seed industry. In developing countries, such as Argentina and in India, such moves were met with resistance. In India, the government resorted to price control and reduced the amount of royalty demanded by Monsanto-Mahyco (Van Dycke & Van Overwalle, 2017). Whether or not the scope of this protection extended to subsequent generations of cultivars became a contentious issue in the US and Canada, where more than one form of IP protection was available.

The TRIPS agreement has also been resisted by developing countries for not sufficiently taking into account cultural, political-economic and ecological dimensions, and for pushing globalization while disadvantaging local practices (McAfee, 2003).

The Cartagena Protocol on Biosafety aims to protect biological diversity from the potential adverse effects of GMOs. It is an international agreement annexed to the 1993 Convention on Biological Diversity, entering into force in 2003. Central to the Protocol is the precautionary principle, which states that a lack of full scientific certainty is no reason to postpone measures to avoid or minimize risks posed by a living modified organism resulting from biotechnology. It allows developing nations to balance public health with economic benefits. The Cartagena Protocol applies to the transboundary movement, transit, handling, and use of all living modified organisms that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health (Article 4 of the Protocol, SCBD 2000). Some major GM crop-producing countries (i.e., the US, Argentina, and Canada) have not ratified the Cartagena Protocol, while others (India and Brazil) have.

Central to regulation of GM foods, plants and crops are containment of risks, transparency, freedom of consumer choice, and marketing issues. Therefore, regulatory regimes lay out rules for risk assessment, risk containment and labeling, and among others. The EU currently has the most harmonized and comprehensive framework for GMOs, covering contained use, field trials, marketing of GMOs, post-market monitoring, labeling, and traceability (Srinivas, 2020). Commercial cultivation of GM crops only occurs in Spain, but large amounts of GM soya and corn are imported as animal feed. Similar to the Cartagena Protocol, the precautionary principle is a fundamental principle of European legislation, and the EU GMO Directive 2001/18/EG is in line with this principle.

Fundamentally, there are two ways for countries to assess the risks of and regulate GMO crops: process based—defining plant varieties based on the process by which they were created, and product based—defining plant varieties based on the properties of the resulting product. The EU is an example of the first: classic mutagenesis

methods, introducing small, random changes to the DNA of crops are exempted from the GMO Directive, because no foreign DNA is introduced. The recent emergence of new genome editing techniques, such as CRISPR-Cas9, allow for the deletion or replacement of single base-pairs, rather than introduction of foreign DNA as in recombinant DNA techniques. In the EU, this has sparked a debate about whether genome-edited crops should fall under the GMO Directive. Proponents argue that genome editing techniques are similar to classic mutagenesis techniques, as no foreign DNA is introduced. Opponents argue that safety for public health and the environment has not been proven. In 2018, the European Court of Justice ruled that gene-edited crops should be considered as GMOs.

The US is an example of the product-based approach to regulating GM food, where regulations are based on the GM foods and how they are used, rather than the technologies that were used to make them. Hence, the safety of GM foods in the US is assessed using the same rules as all other foods, and no special labeling or pre-market approval applies. The introduction of GM plants in the field is regulated by the US Department of Agriculture (USDA) that prevents the spread of (potentially) invasive new plants in the US. USDA requires companies to submit information on the plant, such as field test reports, experimental data, and publication and description of the genotype and phenotype, before GM plants can be planted, and regulates where GM can be transported and how much can be planted. Finally, if GM plants produce insecticidal substances, regulations concerning the effect of pesticides on human health and the environment apply.[6]

According to a survey among 33 countries and the EU, process-based regulations were employed by 15 countries and the EU, among which are Brazil, China, New Zealand, and Australia, whereas 14 countries employed product-based regulation, including Argentina, the US, Canada, the Philippines, and Bangladesh (Ishii & Araki, 2017). Hence, the regulatory landscape for GM foods is fragmented globally, and there is no harmonization of norms and rules of GM foods across the world. A current pressing issue is how different regulatory regimes will react to genetically edited foods. Some countries might choose the option of deregulation of genome edited crops, or treating genome edited crops as equivalent to plant species developed by traditional plant breeding methods, while others might treat genome edited crops as GMOs.

TA work on GM foods

GM foods have long been on the agenda of TA institutes, raising questions concerning biodiversity and sustainability (i.e., Meyer et al., 1998), as well as social consequences (i.e., BAS, 2008). TA has also been concerned with the public and political debate, organizing citizen panels (i.e. TA-Swiss, 1999 and many more, see Einsiedel, 2012, Table 1 for an overview), and monitoring technical and scientific developments. In 2009, the European Parliamentary Technology Assessment (EPTA) network issued a report about the challenges to European policy on GM plants (Bütschi et al., 2009).

[6] See: https://www.usda.gov/topics/biotechnology/how-federal-government-regulates-biotech-plants (accessed 8-4-2022).

These challenges related to new driving forces for GM plant introduction, including agriculture for non-food products such as bioenergy and biomass; the development of new types of GM plants, technologies and applications; public acceptance of GM plants; labeling of GM products, and consumer choice and international trade rules. On each of these issues, the EPTA network provides options for action to policymakers.

In recent decades, public discourse and policymaking have been focused around regulations and issues like food safety and environmental impact. Likewise, the concerns regarding genetically edited crops have also been on governance and regulation (Entine et al., 2021) or on risk assessment (Kawall et al., 2020). Here, discussions have also focused more on specific aspects than on a holistic assessment.[7] One of the aims of TA, however, is to include other impacts of technological developments like GM food, such as economic impacts, environmental impacts, impacts on women, impacts on health, and impacts on labor (Chaturvedi & Srinivas, 2019). TA methods could be helpful to assess such broad impacts of GM foods. Moreover, the issues and impacts of GM foods are not similar for each country: there are different regulations, needs, and cultures in each country. A globalized TA effort can help to gain insight into the broad implications of (the governance of) GM foods for the diverse situations in various countries across the globe, and the impact of globally standardized governance in each of these situations.

3.2 Synthetic Biology

In the early 2000s, synthetic biology (or SynBio) emerged at the center of biotechnology developments. Synthetic biology is the engineering of biology to (re)design organisms or complex biologically-based systems which display functions that do not exist in nature and that are useful for mankind. A fundamental difference between genetic engineering and synthetic biology is that, with the latter, it is possible to redesign a biological system or organism, or to create a totally new organism not found in nature. As such, synthetic biology creates new opportunities and raises new expectations and concerns. Therefore, existing regulatory regimes created for genetic engineering may not be suitable to regulate synthetic biology (Srinivas, 2020). Globally, a Do-It-Yourself biology (DIY biology) movement has emerged making protocols and kits available online, allowing amateurs to experiment with synthetic biology at home. The DIY biology movement is now diverse in terms of geography and location. The international genetically engineered machine (iGEM) competition, held since 2004, provides a platform for novel ideas and experiments in synthetic biology. So far, synthetic biology has not been dominated by multinational corporations and there are strong countervailing forces like the DIY biology movement to prevent this.

[7] For example, see: https://www.europarl.europa.eu/cmsdata/232239/Booklet%20WS%20Genome%20Editing%2015-04-2021_final.pdf.

The global debate and governance of synthetic biology

The discourse about synthetic biology is fueled by its potential benefits, such as the production of medicine by artificial bacteria, biofuel from algae, or developing biosensors that improve measuring instruments. At the same time, synthetic biology raises concerns. How far can we intervene in the living world? Can we foresee the consequences? The international debates relate to issues of biosafety and biosecurity, intellectual property and the international framework on *ethics and human rights.* Across the globe, different discourses relating to innovation, risk, power and control have emerged, involving different actors. In contrast to the first attempts at regulating genetic engineering, which was mainly initiated by experts at the Asilomar Conference, many different actors, including NGOs, have been involved from the beginning, and the need to incorporate stakeholder and public questions and concerns into policymaking has been on the agenda from an early stage (Stemerding & Rerimassie, 2013). Moreover, the global nature of the developments, due to the international interconnectedness of academic disciplines and the industrial sector, has been mentioned as one of the central features of synthetic biology (ibid.). This brings out the need for transnational governance and international coordination. Currently, governance of synthetic biology is evolving, with countries following different approaches (Trump et al., 2020) without moving toward global harmonization. However, the extension of regulatory regimes developed for genetic engineering/GMOs is also emerging as an option. The ongoing discussions under the Convention on Biological Diversity relate to the question of whether synthetic biology would be covered by the Cartagena Protocol on Biosafety (Lai et al., 2019). Synthetic biology was discussed at the Convention on Biological Diversity and the Ad-hoc Technical Experts Group (AHTEFG), but there was no consensus on the assessment of new genetic technologies, such as synthetic biology. Major differences occurred between parties that grow and export GM crops and other parties that take more precautionary approaches. The AHTEFG has proposed establishing a "Multidisciplinary Technical Expert Group on Synthetic Biology to carry out the horizon scanning, monitoring and assessment process" (Third World Network, 2021).

TA and synthetic biology

Synthetic biology is currently receiving much attention from the (institutional/parliamentary) TA community (i.e., EPTA, 2011; POST, 2008, 2014; Stemerding & Rerimassie, 2013; TAB, 2015). Synthetic biology has dual-use potential and there are concerns about *biosecurity,* the potential for misuse and *biosafety*, and the potential unintended consequences of the technology (see: NASEM, 2018). One suggestion has been that prospective TA in combination with ethics is necessary (Schmidt, 2015), or that it can be complemented with an analysis based on Responsible Research and Innovation (RRI) (Stemerding, 2019). One way to go about this is to review the literature and case studies of TA in dual use in other fields such as cybersecurity (e.g. Riebe & Reuter, 2019), and draw lessons from that. Synthetic biology was one of the topics of the Global Ethics in Science and Technology (GEST) project (2011–2014), which compared the role of ethics in science and technology policy

as it was developing in Europe, China and India. But the real challenge lies in using TA in technological convergence: the "tendency of different systems to eventually evolve, blend, and synergistically reinforce and interact with each other, sharing and extracting resources and energy to produce new and unique meta-technological products and outcomes" (McCreight, 2013, p. 12). This convergence has the potential to improve human lives, but also to be put to use in warfare and, as such, have disastrous consequences for the global balance of power. Synthetic biology is often mentioned as one of the technologies that has this potential, together with artificial intelligence, neuroscience, nanoscience and robotics. Utilizing foresight methodologies from TA, such as scenario analyzes and horizon scans, can be helpful in developing governance that anticipates future developments. An example is the techno-moral future scenarios on synthetic biology, developed by the Rathenau Instituut and the 2012 iGEM University College London team.[8] Together, they present a range of possible futures for synthetic biology in our society and in our lives, and support politicians, scientists and the broader public to reflect on the possible positive and negative impacts. This facilitates the conversation between policymakers, stakeholders and the public about what role they envision for synthetic biology in society, and how we can stimulate this through governance while limiting the negative consequences.

3.3 Human Genome Germline Editing (HGGE)

In the first decades after 1970, the assessment of the consequences of biotechnology focused on environmental and health risks and (global) trade, but in the 1990s the assessment of underlying values and the role of ethical principles for the governance of biotechnology became more prominent. As the science of genetic engineering and molecular biology progressed, attention turned toward the engineering of the human genome. In 2003, the entire human genetic code was mapped for the first time, the outcome of the Human Genome Project which had started in 1990 (NIH, 2021). The expanding knowledge of the genetic basis of human traits and disorders, and new technologies for modifying genes, could in time make it possible to alter the building blocks of our lives: human DNA. When the DNA in the cell of a human embryo or in cells that could grow into reproductive cells is modified in the laboratory, we speak of *human germline genome editing* (HGGE). When a child grows out of a genetically modified embryo, the DNA of their offspring will also contain the modification. HGGE could have a variety of social repercussions that require governance with a strong basis in values from society.

[8] See: https://www.rathenau.nl/sites/default/files/2019-01/Future_scenarios_synthetic_biology.pdf.

The global debate and governance of HGGE

In response, international and global agencies have attempted to curtail modifications of the human genome through regulations and treaties. In most countries, human genome editing is prohibited by law (Ledford, 2015). In addition to national prohibitions, various human rights treaties curtail modifications of the human germline, such as the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997), which considers the human genome as "the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity." (Article 1) The Council of Europe addressed genetic modification of the human genome in Article 13 of the Oviedo Convention, stating that an intervention to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes, and only if its aim is not to introduce any modification in the genome of any descendants (Council of Europe, 1997). In the European Union, eugenic practices and cloning of human beings are both deemed to be in violation of human dignity and are rejected in Art. 3(2b) of the Charter of Fundamental Rights (2000). More recently, the European Clinical Trial Regulation (2014), which entered into force in 2019, also prohibits the alteration of heritable DNA by providing that, "No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity." (European Clinical Trial Regulation, 2014, p. 51).

In 2012, a new technology was discovered for modifying DNA: CRISPR-Cas9 (Jinek et al., 2012). In contrast to earlier genome editing technologies, CRISPR is often referred to as a 'molecular scissor'. Scientists regard the technology as 'easy to use, precise and relatively inexpensive'. Within the medical field, scientists, doctors and patients hopefully anticipate the possibility of preventing the transmission of (severe) heritable diseases through HGGE (De Wert et al., 2018; Liang, 2015).This development has reopened the discussion about the modification of heritable DNA.

At the international level, different initiatives to discuss and reflect on human genome editing have been initiated. For example, at the two "International summits on genome editing" in 2015 and 2018[9] experts have discussed the scientific state-of-the-art and the ethical and societal questions, and concluded that it was, at that time, irresponsible to use germline genome editing in a clinical setting, to alter the genetic make-up of future persons. Firstly, because the technology was deemed not safe and efficient enough, and secondly, because of a lack of broad societal consensus about the acceptability of clinical use of HGGE. Despite worldwide consensus that the use of gene editing technologies to modify the DNA of future persons is not acceptable due to ethical concerns, as well as issues with safety and efficacy, and despite that HGGE for reproductive purposes were prohibited, the Chinese scientist He Jiankui announced that the world's first gene edited babies had been born in China on November 26, 2018 (Cohen, 2019). This led to an outburst of reactions from within and outside the academic community, and calls to consider a temporary worldwide ban on the reproductive applications of HGGE until adequate reflection has taken

[9] See: https://www.nationalacademies.org/our-work/international-summit-on-human-gene-editing (accessed 8-4-2022).

place at the national and international levels (i.e. Lander et al., 2019). It soon became clear that many scientists from around the world were aware of He's plans to let babies grow out of genetically altered embryos (Cyranoski, 2019). The announcement by He Jiankui was taken by the Chinese government as an opportunity to enhance the ethical governance of emerging technologies by establishing a National Science and Technology Ethics Committee and issuing the "Regulations on the Administration of the Clinical Application of New Biomedical Technologies", which improved the management system for the clinical application of new biomedical technologies at different risk levels.

In the aftermath of this incident, the WHO founded the advisory commission on Developing Global Standards for Governance and Oversight of Human Genome Editing, that issued a Framework for Governance and Recommendations on the topic in 2021. In this set of documents, the committee gives advice and recommendations on appropriate institutional, national, regional, and global governance mechanisms for HGGE.[10] It recognizes that governance is needed at national and transnational levels, because both the research and the societal effects will go beyond national borders. Therefore, it recommends that the WHO should take leadership and work with others to establish international collaborations for effective governance and oversight. According to the committee, good governance in this context is value-based and principle-driven, and it provides a list of the values and principles that should inform governance decisions. By putting forward seven scenarios, the committee illustrates the practical challenges that can be encountered when establishing good governance of HGGE.

In 2020, the US National Academy of Science and the UK Royal Society International Commission on the Clinical Use of Human Germline Genome Editing issued a report that aims to provide a "translational pathway" from preclinical research to clinical application that governments can use to introduce HGGE in their countries should they decide to permit such use (NAM, NAS, and the Royal Society, 2020). Notably, it also asserts that "extensive social dialog should be undertaken before any country makes a decision on whether to permit clinical use of heritable human genome editing (HHGE)."

Because the current global regulatory landscape regarding HGGE is very fragmented and no global authority that can adopt and enforce binding rules at the global level exists, it is unlikely that a single mechanism will be sufficient. A mixture of different soft-law mechanisms, such as international registries, conferences and (nonbinding) governance frameworks by international organizations such as WHO, and guidelines from professional societies such as the US National Academy of Science and the UK Royal Society will nonetheless be beneficial to develop global consensus about what HGGE activities are ethically unacceptable, and mechanisms to detect and report them (Marchant, 2021).

[10] See: https://www.who.int/news/item/12-07-2021-who-issues-new-recommendations-on-human-genome-editing-for-the-advancement-of-public-health (accessed 8-4-2022).

TA and HGGE

In the early 2000s, the main concern raised by TA was the possibility to read the human genome (PACE, 2001; POST, 2000), and this is still an ongoing debate (POST, 2015; STOA, 2008, 2021). TA institutes have analyzed the possible benefits of these developments, such as more precise characterization of medical conditions, better diagnostics and disease prevention, as well as potential (unwanted) impacts such as the commercialization of (individual) genetic information. More recently, the possibility to edit human DNA has technically become more realistic, with the discovery of "genetic scissors" CRISPR-Cas9. TA institutes have assessed the possible benefits, risks and ethical issues of these developments concerning genome editing in plants, animals and humans (ITA, 2016; POST, 2016; TAB, 2015; Van Baalen et al., 2020), and have been involved in the organization and analysis of broad public dialogs about HGGE (Van Baalen et al., 2021). For this dialog, a set of four techno-moral future scenarios were developed.[11]

4 Public Engagement in Biotechnology and TA

As one of the central aims of TA is to aid the democratic control of developments in STI, participation of a range of stakeholders and the wider public is an important element of TA. This is all the more important for TA of biotechnology, as biotechnology challenges some of the conceptualizations that people use to make sense of the world, such as between sickness, health and enhancement, between living and non-living, between nature and technology, and between biology and engineering. Moreover, over recent decades, the debate has broadened from micro-organisms to plants to human beings (STOA, 2008). As these developments have such a tremendous impact on our bodies, lives and surroundings, they should not be left to driving forces such as science, industries and markets. Rather, policymakers and citizens—the public-should be aware of the developments and enabled to take part in the discussion about their desirability and acceptability.

Moreover, citizens are demanding to have a say in the governance of these developments: from the 1990s onward, biotechnology has increasingly became the subject of public and societal debate, often sparked by single events, such as the creation of Herman the transgenic bull in the Netherlands in 1990, the first commercial production of GM food in the US in 1994, and Dolly the cloned sheep in 1996 (see: Einsiedel, 2012; Hansen, 2011). In the early 2000s, public concern with genetic engineering, most notably genetically modified crops and other food products has had considerable influence on GMO policy throughout the globe. As such, an important task of TA in biotechnology is to include a range of perspectives from the public and societal groups in the assessment of technologies.

[11] See: https://www.rathenau.nl/en/making-perfect-lives/discussing-modification-heritable-dna-embryos (Accessed 8-4-2022).

Box 1. Public Attitudes to Human Genome Germline Editing (HGGE)

Public surveys

Public surveys in China and the US show that 72.5%, 72.8%, and 70.9% of Chinese respondents clearly expressed their support for the clinical use of HGGE to prevent fatal diseases, prevent non-fatal diseases, and reduce the possibility of serious diseases, respectively, compared to 71%, 67%, and 65%, respectively, in the US. Nearly half of the Chinese public supported the clinical use of HGGE for the purpose of enhancement, a larger proportion than that of the American public (48.6% vs. 12%).

An international survey among Canada, the US, Brazil, Germany, Sweden, the Netherlands, the UK, France, Spain, Italy, Poland, Czech Republic, Russia, South Korea, Japan, Taiwan, India, Singapore, Malaysia and Australia (Pew Research Center, 2020a), shows that 70% of participants think it is appropriate to use HGGE to treat a serious disease or condition the baby would have at birth, 60% think it is appropriate to use HGGE to reduce the risk of a serious disease or condition that could occur over the baby's lifetime, and 14% say it is appropriate to use HGGE to make the baby more intelligent. The third scenario evokes the widest diversity of opinions across publics: from 8% percent agreement in Japan to 64% agreement in India.

Societal dialog

In the Netherlands, politicians request societal dialog about controversial topics. In 2019 and 2020, a broad societal dialog to ascertain the views of society towards the clinical application of HGGE was organized by a consortium of Dutch societal partners, financed by the Dutch Ministry of Health, Welfare and Sport (Van Baalen et al., 2021). In general, participants had no fundamental and absolute objections towards HGGE technology. However, they only deemed HGGE to be acceptable when it is used to prevent serious, heritable diseases and under strict conditions, without affecting important (societal) values. A small group of participants found HGGE fundamentally unacceptable because it would cross natural, socio-ethical or religious boundaries. 69% of the respondents agreed with HGGE to prevent a serious muscular disease, 37% agreed with HGGE to protect a child against a serious infectious disease, and 8% agreed with HGGE to make a future child more intelligent (DNA-dialoog, 2021). Compared to the respondents in the Chinese and US studies, the Dutch respondents are more cautious towards the use of HGGE.

Biotechnology and the need to include public perspectives have been an important factor in the establishment of TA-institutions throughout Europe and the development of approaches to TA that emphasize public participation, such as *participatory* or *interactive* TA, and related methodology, such as *consensus conferences* (Einsiedel, 2012). Different issues play a role in these debates. For example, religious beliefs and concepts of nature, health, disease, and parenthood. Members of the public

voice ethical concerns on "messing with nature" or "playing god" when intervening in the fundamental building blocks of plants, animals or humans is discussed (Evans, 2001). But they are also concerned with the direct and indirect risks of using advanced genetic engineering technologies when not all aspects of the biology are known. Can we introduce genetically modified plants or animals safely into the environment? Are GM foods safe to eat? Is it possible that artificially introduced genes may be transferred to natural forms? And does this impose a threat to the natural environment and biodiversity? And how can we make sure that targeted DNA-modification of an embryo (a future child) does not introduce off-target modification. Moreover, the public is also concerned with the interests of other stakeholders: who decides whether these risks are acceptable and who will benefit? Especially in the debate on GM crops, the concentration of power in large, global agrochemical and plant breeding companies is objected to, while in the debate on HGGE, the public is concerned with long-term social consequences, such as the genetic consolidation of pre-existing socio-economic inequalities (Van Baalen et al., 2020; Habets et al., 2019).

Despite these concerns, almost all the scientific associations and UN organizations such as FAO and WHO are assured that GM foods are safe. More importantly the reports (i.e., FAO, 2004; NAS, 2014; Nuffield, 1999) point out the need to take into account concerns related to ethics and values and urge greater engagement with the public and better communication on risk and benefits. A report about TA on converging technologies by STOA (Panel for the Future of Science and Technology at the European Parliament) concludes that "there was a need for values and criteria" and that "almost all agreed on a need for more public input" because "there is still little awareness about converging technologies despite their far-reaching potential." (STOA, 2006, p. V) The biotechnology patent debate revealed deep moral concerns about basic genetic research that should be taken into consideration by TA. To adequately address moral and public concerns, a more contextual approach is needed, which integrates various forms of interaction between biotechnology and society (Hoedemaekers, 2001). Given the importance of ethics and public consultation and engagement, many tools and methodologies have been identified or developed, and put into practice, such as citizens' forums, consensus conferences, focus groups, public hearings, and scenario workshops (see Beekman et al., 2006 for different decision-making frameworks and public consultation methods).

Box 2. Public Perception of GM Food and Crops in China and Worldwide

The acceptance of GM food and crops by the Chinese public has consistently declined over the past decade. In 2000, 83% of Chinese consumers were willing to buy nutritionally improved GM food, registering the highest proportion among the ten countries surveyed (FAO, 2004). In 2006, the proportion of Chinese urban consumers accepting GM food was about 65% (Huang et al., 2006), and in 2011, 42.1% of the respondents clearly support the promotion of

genetically modified rice in China (Guangxi et al., 2015). In 2016, 63.2% of the respondents opposed the promotion of GM rice in China and only 27.1% expressed their support; 74.1% of the respondents were reluctant to eat GM food, compared to only 17.8% who were willing.

An international survey in publics across Europe, the Asia–Pacific region, and in the US, Canada, Brazil and Russia finds that across the globe, a larger proportion of the public thinks that GM foods are unsafe to eat than the proportion that think that GM foods are safe (Pew Research Center, 2020b).

Some information on the public perception of HGGE (Box 1) and GM foods and crops (Box 2) is presented. Although these only cover a few countries, and much more can be said about the public perception of these technologies, the information in these boxes shows three things. First, public perceptions differ from country to country. Generally, the attitude of Christians, especially those in the West, are more cautious toward HGGE than religiously unaffiliated people, although acceptance of HGGE is not uniformly linked with religion. For example, Hindus and Muslims in India are equally likely to view research on HGGE as appropriate (Pew Research Center, 2020a). The Chinese public, under the influence of the pragmatist cultural tradition, generally show a higher acceptance of new biological technologies. These differences are also reflected in the way ethics related to such new technologies are managed: in China this is driven "top-down" by the government.

Second, surveys on HGGE broadly show similar patterns: that modifying the genetic traits of offspring is controversial, and its acceptance depends on the purpose of the application. Preventing serious heritable disorders is regarded as an acceptable application more often than human enhancement. However, the outcomes of surveys disguise more nuanced considerations that will be useful for political decision-making. For example, from societal dialog in the Netherlands a set of values were derived that need to be protected in policy-making. These are: safety/precaution, the prevention of suffering or illness, protection of early human life, respect for the autonomy of the future child, autonomy, accessibility, diversity, inclusivity, non-discrimination, equality and solidarity (Van Baalen et al., 2021). Finally, the declining public acceptance of GM foods and crops in China shows that public perception is not stable and can change over time (see Box 2), for example, in response to public controversies.

How ethics, values, risks, and benefits are considered and what role they play in the public perception of these technologies differs from country to country and over time. This is a challenge for the global governance of biotechnology, as public perceptions of these technologies have played a major role in the resulting regulations in place in different countries. Developing an overarching governance system that takes into account the various perspectives across the globe will be a major challenge and is possibly not feasible. However, an effort should be made to coordinate the different systems of governance in such a way that it allows for variations across countries and regions. For this, forms of participatory (pTA) can be employed to

include a range of (informed) deliberations, perspectives, concerns, and values from members of society in the policymaking process (Hennen, 2012).

5 Global TA of Biotechnology: The Way Ahead

The analysis of three key topics in biotechnology shows that a central feature of biotechnology is that the science is evolving globally and the products that it brings forth are traded across the globe. Yet, there are major differences between the regulation and governance of the academic and industrial sectors between countries. These stem from different needs and interests per country, as well as differences in traditions, cultural differences and public perceptions. To develop an integrated global TA framework on biotechnology the following have to be considered.

International trade

As we have seen, there are different approaches to risk assessment of GM products and emerging biotechnology developments such as gene-edited foods and synthetic biology. WTO agreements aim to bring coherence, in order to facilitate international trade. For example, the technical barriers to trade (TBT) agreement's objective was developed to ensure that technical regulations, standards, and related assessment processes are non-discriminatory, while enabling countries to set suitable standards to ensure protection of the environment and human health. Countries are expected to have international standards as the basis for regulation and base their risk assessment on scientific evidence. Similarly, the objective of the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) is to strike a balance between the rights of governments to protect food safety, plant and animal health on the one hand and these measures becoming unjustified trade barriers on the other. But in practice, this has become a contentious issue. A classic example is the European Community's (EC) Measures Affecting the Approval and Marketing of Biotech Products (Biotech Dispute) case, in which SPS measures pertaining to seven products containing genetically modified organisms were questioned by the US and other countries. At the heart of this case was the use of the precautionary principle by the EC and disputes over interpreting and implementing "science-based risk assessment". Although the dispute settlement body of WTO did not agree fully with the EC's arguments in this regard, the case did not bring in any change in the policy and practice of the EC on imports of GMOs or in risk assessment.

Such disputes show that harmonization of standards and consensus on science-based risk assessment are very difficult to achieve. According to Islam (2019, 16), "The SPS Agreement has not yet addressed the weaknesses of its international standardizing bodies, the inherent tension between the evolving nature of scientific research and the conclusiveness of scientific evidence in assessing risks and the implementation difficulties faced by developing countries with limited or no scientific capability". In short, the SPS agreement, relying on scientific evidence as a conclusive risk assessment criterion, falls short in addressing scientific uncertainty

surrounding biotech products (ibid). The differences in risk assessment arise on account of applying the precautionary principle, setting higher standards in the name of protecting human health and environment, and policies on regulation of risk. The international standardizing bodies set levels, and when a country considers them to be too low, if it thinks that it should set a higher standard it has the option to do so. For example, the Appellate Body took the position in the Beef Hormones dispute that the CODEX international standard was not mandatory and WTO Members could opt for a scientifically established standard that was higher than that of CODEX. So, in case of biotech products, risk assessment, application of the precautionary principle and standards are issues. A European consortium has recently analyzed how the precautionary principle is applied in the European Union, how it relates to innovation and how its future application can be improved.[12]

In addition, the issue with the TRIPS agreement, which is meant to make the development and trade of biotech products profitable through patents, is that it mostly seems to benefit large companies in richer parts of the world while disadvantaging small farmers and local businesses in poorer parts.

Differences in regulations

Global governance of biotechnology is likely to be caught between the process-orientation and precautionary principle of the EU and product-oriented regulation by the US. At the same time, many countries follow their own mode of governance which differs from both. For example, in crop genome editing, Canada follows an approach that is centered on novel traits to regulate. Argentina has developed its own approach to crop genome editing (Lema, 2019). Using the definition of living modified organisms (LMO) in the Cartagena Protocol as the basis, Argentina uses the criteria of whether the crop is a GMO or not. According to Lema, "the Argentine regulation calls for any crop developed using gene editing to be presented to the biosafety commission in order to establish, case by case, if it is GMO or not. This determination is mostly based on the changes present in the genome of the plant intended to be introduced in the market, i.e., the final stage of the breeding process" (p. 148).

The challenges for global governance are many. Should older approaches like product-oriented regulation and process-oriented regulation be applied with modification, or should genome edited crops be regulated as "'normal" crops developed using traditional plant breeding varieties? Risk assessment is likely to be an issue, as treating them as equivalents of crops developed using traditional plant breeding varieties without doing assessment for specific risks will be contested. The scope for countries developing sui generis frameworks cannot be ruled out. Differences in consumer acceptance, labeling requirements, and co-existence are other issues that have implications for global governance.

[12] The results will soon be published on their website: https://recipes-project.eu/. A comprehensive description of case studies on CRISPR-based gene drives and GMOs can also be found on their website.

Cultural variation and different value-systems between countries

Regional cultural variations and differences in underlying values of governance between countries and regions result in variations in how biotechnologies are valued and assessed. This makes it difficult to define rules and regulations that are acceptable to all nations. It also leads to issues such as ethics dumping (Schroeder et al., 2018), in which scientists revert to countries with more lenient regulations or less governance capacity to perform experiments that are not permitted in their own country, and moral free-riding, where countries benefit from R&D that is permitted in their country for moral reasons. An example of the first is the "three parent baby" that was born in New York in 2016. Because the method that was used ("spindle nuclear transfer") was not approved in the US, the doctor went to Mexico to perform the procedure.[13]

Difference in countries' capacities

Not all countries have similar capacities in R&D or utilizing biotechnology innovations. Hence, biotechnologies are unevenly adopted across the world, and different countries may have adopted different generations of biotechnology. This also leads to differences in issues that need to be addressed by governance and regulation. This is also a challenge for a globalized TA: As biotechnology has been unevenly adopted across countries in terms of applications, research in biotechnology and adoption, context-specific TA may be more relevant than global TA.

There is not much literature on TA and biotechnology in developing countries, as TA is generally weakly institutionalized in developing countries. A case study on public engagement with decision-making on Bt Brinjal in India shows the divide between scientists who were in favor of approving it for commercial use and, civil society groups (amongst others) opposing it (see also Srinivas and Van Est, this volume). According to Pandey and Sharma, "As a result, the exercise ended up being an exception rather than constituting a norm and the scientific establishment reverted back to mechanisms of communicating the "right" information to the public through "proper" channels, so that they can make decisions that follow a techno-economic rationality" (Pandey and Sharma, 2020, 164).

Public engagement

Other challenges to the global governance of biotechnology are the moral dilemmas and public concerns raised by developments in the various fields. Public engagement and social debate are required, but are difficult to organize on a global scale, and it is questionable whether or not it is feasible to define a set of values and principles that take into account all existing cultural and social perspectives. TA, especially forms of pTA, can be beneficial by analyzing the possible societal impacts, providing methods for stakeholder and public participation, and uncovering the national and international value-systems that play a role in policymaking (Hahn & Ladikas, 2019). But applying pTA globally may turn out to be challenging given the lack of TA in

[13] See: https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/ (Accessed 8-4-2022).

biotechnology in many countries. National TA institutes can play a role here by attuning their public engagement approaches to each other and by attempting to find shared values underlying public perspectives on biotechnologies.

Conclusion

In conclusion, as global governance is fragmented with little scope for harmonization, global TA of biotechnology can bring clarity, better understanding, and enable better governance. In order to do so, an integrated global TA framework should find ways to address the differences in risk assessment and other relevant regulations between countries, often stemming from cultural differences and different underlying values. Furthermore, different countries are in different stages of adoption and development of biotechnology, focus on different sectors and applications of biotechnologies, and have different capacities for R&D and implementation of biotechnologies or performing TA. Moreover, emergence of new GM food technology, genome editing and synthetic biology have complicated matters, as countries approach governance of these in different ways, with some approaches borrowed from experiences in regulating genetic engineering-based biotechnology. These issues will make the development of a globalized TA framework and collaboration between TA-institutes across countries challenging.

Addressing these challenges will only be possible if there are country-level and regional-level initiatives to 're-invent' a TA of biotechnology. Rather than focusing on harmonization of governance, a global TA of biotechnology should focus on assessing the impact of developments and decisions in one country to other countries, and clarifying both differences and common grounds between countries, for example when it comes to values underlying public perspectives on biotechnology topics or the use of the precautionary principle to assess risk and warrant safety. TA institutes across the globe can work together to fill the gaps in global governance of biotechnology by coordinating their efforts toward national and international governments to ensure that developments are acceptable for all, regardless of cultural differences, and help make sure that countries are not faced with "faits accomplis" due to globalization and rapid developments elsewhere.

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