New Genetic Engineering Techniques: Precaution, Risk, and the Need to Develop Prior Societal Technology Assessment

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Business has been arguing that governments should override the precautionary principle in favor of an "innovation principle." The new genetic engineering techniques (sometimes called "new breeding techniques")[1] provide the perfect cover for this argument. Proponents assure us that these new techniques are essential to address the crises we face and will provide economic benefit, as long as we set aside the precautionary approach that they claim increasingly hampers technological progress. We are in the midst of powerful high-risk technological developments with potentially severe and irreversible health, environmental, and societal implications. It is vital to develop processes for examining new technologies while they are still being developed. We argue that precaution needs to guide technology development in this area. Indeed, it should precede the technology development. An adequate technology assessment and decision-making process requires concerted effort, courage, and restraint, and it must include the option to decide against developing or deploying some technologies altogether.

The first generation of genetically modified organisms (GMOs, or genetically engineered organisms) that emerged around 20 years ago was somewhat cumbersome. It required isolating genes from the DNA of one organism (whether the same or a different species); combining them with regulatory elements of other species; adding a marker gene; sticking all the pieces together as a "gene cassette"; inserting this cassette into a bacterial ring of DNA (called a plasmid); and transferring it into bacteria to multiply many copies. Then it was necessary to get it into the plant or the animal by using specific vehicles or methods of transfer.

In plants the common choices are either to use a specific bacterium as a "transport shuttle" (agrobacterium-mediated transfer), or to load tiny gold or tungsten beads with hundreds of copies of the gene cassette or the plasmid rings containing the cassette and literally shoot them at the plant cells (gene-gun technique or biolistics). The result is integration of the cassette, parts of it, or multiple copies of it, at random places within the DNA of some of the cells, often with substantial injuries (mutations) at the insertion site, and always potentially disrupting a gene. Additional injuries are also observed at random places in the DNA, for example, where the cassette tries to "enter" and integrate.

Plants pose an extra challenge here. They have thick cell walls, do not readily regenerate from differentiated cells,[2] and require additional stages: preparing and cultivating cells,

[1] The biotech lobby, organised in the "NBT Platform," has aimed to rebrand the new GM techniques as "new breeding techniques" to make them sound different from "genetic engineering" and more like traditional plant breeding. The term is often used by the European Commission and other regulatory bodies, although not consistently.

[2] Differentiated cells are fully developed and specialised cells and are no longer "omni-potent."

ensuring de-differentiation and finally regrowing transformed cells into whole plants. Additional hormones and chemicals are required for these different stages. Such types of tissue culture are known to induce numerous mutations (injuries) in the DNA of the organism. The whole spectrum of injuries is referred to as "transformation-induced mutations."[3] Mutations may be large or small insertions, deletions, translocations, inversions, or replacements. All of these have been reported as a consequence of plant transformation, and the number of mutations may be in the hundreds. As detailed later, such mutations also occur with the new genetic engineering techniques.

Mutations can be neutral, bad, or even good, depending on where they occur and what the environmental circumstances are. Any mutation has the potential to have unintended effects that may be problematic, or even deleterious. Size is not a determining criterion; mutations as small as one DNA letter (a point mutation) can result in missing or malformed proteins with potentially severe consequences.[4] In humans, for example, a "point" mutation is enough to cause hemophilia, cystic fibrosis, or sickle-cell anemia. In the production of GMOs, there are many stages in the whole process where something unforeseen may occur. For example, the inserted DNA sequence might affect the regulation and expression of other genes in the organism, leading to unexpected effects. It is thus insufficient to only assess the intended trait (e.g., herbicide tolerance, production of insecticidal Bt toxins, or extended shelf life) for potential negative impacts on human or animal health and the environment.

This emerging understanding of potential harm led to two regulatory responses.

Process-Triggered Risk Assessment

The first regulatory response was the recognition that the process of genetic engineering itself can give rise to unintended changes at the DNA level. Potential negative effects can therefore not be assessed on the basis of the intended trait alone, such as herbicide tolerance, production of insecticides (e.g., Bt toxins), or nonbrowning of fruit. Instead, the DNA changes induced by the transformation processes as well as the unintended effects of the inserted DNA sequences (e.g., interfering with the regulation of the organism's own genes) must be taken into account. Thus, the trigger to initiate the risk assessment procedure has to be the process that was used to produce the organism. This means following a process-triggered approach to risk assessment on a case-by-case basis—that is, each GMO will have to be assessed separately. The international community agreed to this approach in 2000 when finalising the Cartagena Protocol on Biosafety, which is a legally binding treaty for its Parties. One hundred and seventy countries are now Parties to this protocol, while the United States and Canada (both Non- Parties) use product-triggered rather than process-triggered risk assessment. However, the new genetic engineering techniques provide industry with a fresh opportunity to push the Parties to the Protocol, especially Europe, toward product-based assessments.

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[3] A. K. Wilson, J. R. Latham, and R. A. Steinbrecher, "Transformation-Induced Mutations in Transgenic Plants: Analysis and Biosafety Implications," Biotechnology and Genetic Engineering Reviews 23 (2006): 209–37, http://econexus.info/publication/transformation-inducedmutations-transgenic-plants; A. K. Wilson, J. R. Latham and R. A. Steinbrecher, "Genome Scrambling—Myth or Reality? Transformation-Induced Mutations in Transgenic Crop Plants," EcoNexus Report, October 2004, http://econexus.info/sites/econexus/files/ENx-Genome-Scrambling-Report.pdf.

[4] Point mutations can shut down or "knock out" the expression of a whole gene (result: no protein), change the "reading frame" of a gene (result: new or different protein), or change the instruction for one crucial amino acid (result: destroy the function of a protein).

The Precautionary Principle

The second result was the recognition that a precautionary approach should be taken in regulating GMOs, given the uncertainties and the potentially serious negative impacts.

The precautionary principle was established in 1992 as "Principle 15" of the Rio Declaration on Environment and Development.[5] It basically states that where there are threats of serious or irreversible harm, lack of full scientific certainty shall not be used as a reason to postpone cost-effective measures to prevent environmental degradation. Principle 15 can be seen in close association with Principle 13, i.e. the Polluter-Pays-Principle. In this approach, responsibility and scientific knowledge and understanding, including lack thereof, are tightly interlinked.

The precautionary principle is a fundamental ingredient not only in European Union (EU) legislation but also in the Convention on Biological Diversity (CBD) and its Cartagena Protocol on Biosafety. This protocol puts the precautionary principle into operation through its substantive provisions regarding GMOs.

It is important to recall that the precautionary principle was not born out of risk aversion, but out of a history of "late lessons from early warnings." In the report of the same name[6] there are many cases where early indications of harm were neglected with serious consequences. One of the most graphic is that of asbestos, where the first warnings were given in 1898, with serious illness and deaths reported soon after. As asbestos was a highly successful and commercially valuable product, action was only finally taken a century later, with the United Kingdom banning its use in 1999, and Canada only doing so in 2018.

When looking at precaution in the context of GMOs, we have to remember that these organisms are living systems with the ability to self-replicate and spread their genes far and wide through pollen and seed, and thus bring additional levels of uncertainties and risk.

The New Genetic Engineering Techniques

The genetic engineering of the 1990s enabled scientists and GMO developers to break through species and kingdom barriers that until then had kept certain traits and genes and species apart. This is not only an issue for risk assessment of the individual GMO, but should also be seen in the context of evolution and co-evolution, ecosystem functions and services, niches, and webs.

Early genetic engineering enabled scientists to take DNA from one species and insert it into the DNA of a completely different one (now called transgenesis), or to take DNA from the same or a closely related species and insert it (now called cisgenesis and intragenesis). However, the insertions were random, as discussed earlier, and the techniques were costly, slow and inefficient.

The development of new genetic engineering techniques has significantly increased the ease and speed of creating genetically modified organisms (GMOs), while costs have gone down. Scientists are able to make deeper and more complex changes to the genetic makeup of living

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[5] http://www.un.org/documents/ga/conf151/aconf 15126-1annex1.htm.

[6] EEA, Late Lessons From Early Warnings: The Precautionary Principle 1896–2000, Environmental Issues Report No 22, European Environmental Agency (Copenhagen 2001) http://www.eea.europa.eu/publications/environmental_issue_report_2001_22.

organisms. DNA can be rapidly sequenced, and DNA strands can easily be synthesised, often taking digital sequence instructions directly from the internet. This has led to the emergence of two new fields of genetic engineering that overlap with each other: synthetic biology (or synbio) and the so-called new breeding techniques (NBTs). In most cases both involve the use of old-style genetic engineering, but they also go much further.[7]

Clearly new and common to both is the genome-editing tool CRISPR/Cas, which is basically a set of molecular gene scissors designed to cut DNA strands at chosen recognition sites. (The "CRISPR" part is an RNA[8] strand responsible for finding the target DNA; it is attached to the Cas protein, which cuts through the DNA once docked to the target site.) When cut, the cell's own DNA repair system will attempt to stick the severed strands back together again, usually losing, adding, or altering a few letters in the process, thus creating small mutations at the target site. The CRISPR/Cas technique is comparatively cheap, easy, and fast and is therefore attractive to many researchers for altering the DNA at specific sites of interest.

Yet again there are unintended effects. At times the DNA scissors will cut off-target, potentially disrupting other genes or changing their levels of expression, resulting in missing or malformed proteins or even new proteins, or altering the function of a protein.

Off-target mutations, mostly identified in areas that have similarities (homologies) to the target sequence, have repeatedly been reported by researchers. In fact, researchers have developed an assumption that off-target effects will only occur at DNA sites that are similar to the target site, and that these mutations will be small insertions or deletions (termed "indels"). Researchers have developed algorithms based on the genome sequence of an organism to predict the likely off-target sites, which are commonly the only sites checked for unintended mutations. However, the calls for whole genome sequencing (WGS) to prove rather than simply assume that there are no off-target effects, are becoming louder. A recent paper has sent alarm signals. Whole genome sequencing of mice treated with CRISPR/Cas found hundreds of mutations outside the predicted areas of sequence similarities, and the authors suggest that CRISPR/Cas may be responsible for these.[9] The publishers of the article have been requested to retract it for reaching the wrong conclusions after the stock of two companies working with CRISPR/ Cas9 fell as a result of its publication. However, whatever the merits of the research, the authors were right to criticise the reliance on algorithms to minimise checking for mutations, and to look at the whole genome. Rather than trying to silence unwelcome outcomes, such research needs to be repeated and enlarged. If CRISPR/Cas9 is to be widely used, we had better know its side effects, and use whole genome sequencing to run the tests.

The on-target changes, that is, the intended changes, may also have unintended or unexpected effects, as high-lighted by Doudna, one of the developers of the technique.[10]

Finally, there are a number of ways to get the pre-designed and pre-programmed scissors into the cell. Usually the cell will have to produce the scissors itself and the instructions need to

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[7] See also H. Paul, E. Buecking, and R. A. Steinbrecher, " 'New Breeding Techniques' and Synthetic Biology— Genetic Engineering by Another Name," The Ecologist, April 4, 2017.

[8] RNA: a nucleic acid found in all cells, similar to DNA but single stranded, mostly involved in the production of proteins.

[9] K. A. Schaefer et al., "Unexpected Mutations After CRISPR–Cas9 Editing In Vivo," Nature Methods 14, no. 6 (2017): 547–48. doi:10.1038/nmeth.4293; see also https://phys.org/news/2017-05-crispr-gene-hundredsunintended-mutations.html.

[10] D. Baltimore et al., "A Prudent Path Forward for Genomic Engineering and Germline Gene Modification." Science 348 (2015): 36–38.

be inserted via a DNA "gene cassette" on a plasmid ring. Thus, it is still often necessary to use tissue culture and gene cassette delivery systems, likely giving rise to the aforementioned process-triggered "transformation-induced mutations."

Technical Potentials of the New Techniques

Genome editing tools can be used for three different outcomes: gene disruption, gene correction or alteration, and gene addition.

Gene disruptions (often called "knock-outs") and small random mutations at predetermined sites are easily done with CRISPR/Cas. The next two levels are increasingly difficult, especially the third, the insertion of longer DNA sequences into a predetermined place. New designs of gene scissors are being tried that may be more effective for inserting genes, such as CRISPR/Cpf1. It is still far from certain, however, that such genetic modifications can readily be achieved, especially in plants.

It is also important to remember that CRISPR can be used repeatedly, targeting a number of genes one after the other or in parallel. By disrupting a number of different genes there is the potential to alter or eliminate whole functions or functional pathways, thus changing an organism profoundly. This depth of interference means it becomes an application of synthetic biology, with additional sets of risks and questions.

Synthetic biology[11] (synbio) frequently aims to remodel metabolic pathways, the specific chemical processes occurring within a cell. This can lead to very different or almost new organisms. Several synbio projects aim to redesign microorganisms, for example, for the production of transport fuels, plastics, chemicals, or fragrances. The frequent automation of synbio procedures makes it possible to produce thousands of slight variations on a vast number of individuals of one species almost simultaneously. The sheer volume and mechanisation of the process distinguishes it from old-style genetic engineering, but fundamentally it is still genetic engineering.

Gene Drives

The newest technical development is that of gene drives, a technology designed to eradicate whole populations or entire species, to alter and engineer ecosystems and spread altered genes and traits with unprecedented speed. The idea is actually some 50 years old, but it is the arrival of CRISPR/Cas that has provided the technical capacity to put it into practice.

In 2014 it was still a theory, with Esvelt— one of its developers—warning that this technology urgently required wide societal and safety discussion and deliberation.[12] Only one

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[11] "Synthetic biology is a further development and new dimension of modern biotechnology that combines science, technology and engineering to facilitate and accelerate the understanding, design, redesign, manufacture and/or modification of genetic materials, living organisms and biological systems." This text was prepared by the CBD AHTEG on Synthetic Biology in September 2015 as an operational definition, and the CBD decided at COP-13 it considers the text useful as a starting point for the purpose of facilitating scientific and technical deliberations under the convention and its protocols. https://bch.cbd.int/synbio/.

[12] K. M. Esvelt, A. L. Smidler, F. Catteruccia, and G. M. Church, "Concerning RNA-Guided Gene Drives for the Alteration of Wild Populations," eLife July 17 (2014): 3. pii: e03401. doi:10.7554/eLife.03401.

year later, research papers started to appear detailing the first functioning gene drives for yeast, fruit flies, and mosquitoes.

Gene drives are designed to override the Mendelian 50:50 rule of inheritance, where any gene of a parent has a 50% chance to be passed on to the next generation. As a result, the designated gene or trait, for example, female sterility, has an almost 100% chance of being passed on to every member of the next generation, thus rapidly spreading through a population.

Suggested applications range from agricultural uses—making weeds that have become resistant to herbicides susceptible again; eliminating agricultural pests, such as the invasive Palmer amaranth, or fruit flies in California damaging soft fruit—to conservation uses, for example, to eradicate invasive mice that endanger bird species on islands. Anything that reproduces sexually is a potential target for gene drive applications, from mosquitoes carrying pathogens to carp species invading new ecosystems.[13]

The ability to release a gene drive organism with the intention to alter or eradicate a wild population or a whole species provides a very powerful tool. It has the potential to alter whole ecosystems and their functions and services.

No species live in isolation; all are part of the various networks and food webs that make up an ecosystem. What is an alien invasive species or a pest in one context may be an integral part of ecosystem functions and services in another context. It is particularly important to fully and thoroughly assess gene drives because they are not designed for contained use in laboratories or factories; they are intended to spread through ecosystems.

In order to fully understand and predict the consequences of the release of a gene drive organism, we would need to appreciate the role this organism (species) has in different ecosystems, habitats, and environments. We also need to understand what cascade effects could result from altering this species or taking it out of the web of life.

At present, we do not have the knowledge or the capacity to address these issues or predict the outcomes of intentional or accidental release. As such, no releases—intentional or accidental— should take place until we can ascertain the consequences. The risks are too high. We need to apply the precautionary principle and agree to a moratorium to give us the time to perform all the necessary tasks and debates and establish the necessary rules and procedures of international governance.

The Importance of Precaution in Risk Assessments

Precaution requires us to take broader perspectives and avoid too narrow a focus. In this issue, Anne Chapman covers both the ethics and the politics of this theme. When assessing risks, it is essential to look at both direct and indirect effects. As first-generation GMOs already showed, the trait of herbicide tolerance can have profound impacts on the environment, human health, biodiversity, and socioeconomic conditions. The herbicide spraying regimes as practiced in the large RR-soy monocultures in South America have led to severe negative impacts, with medical doctors reporting increased rates of cancer and birth

[13] The National Academies of Sciences (USA), Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values, report (Washington, DC: 2016), http://www.nap. edu/23405.

defects in affected areas.[14] Indirect effects may involve anything from health impacts or biodiversity loss due to repeated applications of herbicides, the manifestation of secondary pests, or changes in agricultural practices, to loss of genetic diversity and further intensification of monocultures. They may relate to loss of soil and soil fertility, soil compaction, depletion of water, and loss of resilience.

One of the biggest issues with the new technologies is that they claim to be able to solve problems without taking into account environmental implications, biological and ecological limitations, or societal context. The approaches taken are increasingly linear. Real solutions should involve system approaches that attempt to strengthen resilience in agricultural systems, increase buffer capacity and biodiversity, build up soil fertility, create and maintain microclimates, and build systems that minimise occurrence and impacts of floods, erosion, drought, or heat. There are integrated approaches that can do this, but these are not the new techniques under discussion here. (See, for example, the IAASTD report[15] and IPES-Food report.[16])

Increasing Pressure to Set Aside the Precautionary Principle

The multiple ecological and social crises we face (climate change, environmental destruction, loss of biodiversity, social injustice) are being used to pressure governments and move public opinion to support innovations such as the new genetic engineering techniques, including gene drives. It is claimed that these crises demand that we take greater risks, because whatever might go wrong with the technologies will be minor by comparison with the multiple threats of rapid climate change, rampant vector-borne diseases, and famine. We are also told that we need to develop yet another layer of technologies to deal with these crises, rather than addressing the actual causes. This means that hostility to the precautionary principle is being cultivated just as new techniques are emerging with the power to make deeper and wider changes to living organisms than we have ever seen. This has very dangerous social and environmental implications.

Precaution Versus an Emerging Innovation Principle

Impatient with regulation, some governments and corporations argue that the precautionary principle hampers innovation and the economic progress assumed to accompany it. They want regulation and precaution to be "balanced" against a so-called "innovation principle." Twelve chief executive officers (CEOs) of major multinational companies, including Bayer, BASF, Dow AgroSciences, E.I. du Pont de Nemours, and Novartis, signed a letter in October

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[14] M. Vazquez, E. Maturano, A. Etchegoyen, F. Difilippo, and B. Maclean, "Association Between Cancer and Environmental Exposure to Glyphosate," International Journal of Clinical Medicine 8 (2017): 73–85. doi:10.4236/ijcm.2017.82007. Declaration of the 3rd National Congress of Physicians in the Crop-Sprayed Towns, Faculty of Medicine, University of Buenos Aires, Buenos Aires, Argentina, October 17, 2015, http://reduas.com.ar/ declaration-of-the-3rd-national-congress-of-physiciansin-the-crop-sprayed-towns/#more-1541.

[15] IAASTD, Agriculture at a Crossroads, International Assessment of Agricultural Knowledge, Science and Technology for Development. Global Report: 2009, http://www.fao.org/fileadmin/templates/est/Investment/Agriculture_at_a_Crossroads_Global_Report_IAASTD. pdf.

[16] IPES-Food, From Uniformity to Diversity: A Paradigm Shift From Industrial Agriculture to Diversified Agroecological Systems, International Panel of Experts on Sustainable Food Systems, 2016, http://www.ipes-food.org/images/Reports/UniformityToDiversity_FullReport.pdf.

2013 to the presidents of the three EU institutions proposing adoption of the innovation principle.[17] They regard this as necessary due to the "negative impact of developments in risk management and regulatory policy on the innovation environment in Europe." They request that "whenever policy or regulatory decisions are under consideration, the impact on innovation should also be fully assessed and addressed."[18]

This effectively means that they are asking for real risks to be evaluated in balance with possible future benefits. The innovation principle is presented by Business Europe, the European Risk Forum, and the European Roundtable of Industrialists as necessary to attract investment and to ensure that Europe does not fall behind in innovation.[19] However, the effect of applying it would be increased freedom to release new and old products on the market as rapidly as possible. It is not clear how it would be put into practice, but for industry it is yet another instrument to combat unwelcome rules or decisions.

Resistance to Precaution at the International Level

As noted in the preceding, there is growing resistance to the application of the precautionary principle at the international level, from states such as the United Kingdom, the United States, and Brazil, as well as groups such as the International Chamber of Commerce (ICC), the Biotechnology Industry Organisation (BIO), the Public Research and Regulation Initiative[20] (PRRI), and the European Risk Forum (ERF). At the last meeting of the Parties to the Cartagena Protocol on Biosafety, this resistance showed itself in a new level of aggression from promoters of genetic modification (GM) and new genetic engineering (GE) techniques with serious consequences for a key international regulatory initiative. The Ad Hoc Technical Expert Group on Risk Assessment and Risk Management, which was a critical part of the process to examine new GM techniques, was actually closed down, while its Guidance on Risk Assessment of Living Modified Organisms[21] came under severe criticism for being too precautionary. This has serious implications for the application of precaution and the obligations of states under the Cartagena Protocol to adequately assess the risks of GMOs.

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[17] Claude Juncker, on the Innovation Principle, November 4, 2014, http://www.riskforum.eu/uploads/2/5/7/1/25710097/innovation_principle_letter_4_nov.pdf.

[18] European Risk Forum (ERF), The Innovation Principle: Question & Answers, March 5, 2015, File: Innovation Principle Q&A, http://www.riskforum.eu/ innovation-principle.html (http://www.riskforum.eu/uploads/2/5/7/1/25710097/innovation_principle_q&a_5_march_2015.pdf).

[19] BUSINESSEUROPE, the European Risk Forum and the European Round Table of Industrialists: Better Framework for Innovation—Fuelling EU Policies with an Innovation Principle, Joint Statement 2015, http://www.riskforum.eu/innovation-principle.html & http://www.riskforum.eu/uploads/2/5/7/1/25710097/business europe-erf-ert_innovation_principle_joint_statement. pdf.

[20] Corporate Europe Observatory, "How Public Are the Public Research Lobbyists of PRRI?", Briefing for CBD COP/MOP (Bonn, Germany, 2008), https://corporateeurope.org/sites/default/files/sites/default/files/resource/prri.pdf.

[21] Secretariat of the Convention on Biological Diversity, "Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment," Biosafety Technical Series 04 (December 2016).

Beginning a Process of Prior Societal Assessment of New Technologies

The Precautionary Principle: Assessing Potential Harm Before Technologies Are Fully Developed or Deployed

"The more people get to know about GM the more certain they become that no one knows enough."[22]

It seems inevitable that human beings will continue to increase their technical capacity to intervene in natural systems and to alter them. However, as technologies become more powerful, does society have the means and tools to make wise decisions about whether and how to use them, and how to control their development and deployment by corporations? We would argue that it currently does not. We therefore need to find a way of examining emerging technologies to assess their potential for harm before they are fully developed or deployed. This requires a process based on precaution and work with a wide range of people including scientists, sociologists, philosophers, politicians, and the general public. It is particularly important to consult with Indigenous Peoples and local communities who have their own knowledge systems and cultural references.

In the United Kingdom, there have been two societal dialogues on the regulation of these new technologies, the GM Nation debate in 2003 on genetic engineering[23] and the Synthetic Biology Dialogue in 2009–2010.[24] The first involved discussions between self-selected members of the public and specialist critics and proponents of GM and revealed a clear desire for "impartial, worldwide regulation." The second showed that the members of the public (as represented by a group carefully selected to have as few biases as possible, even excluding members of any environmental NGOs) were skeptical about the promises made for synthetic biology. Many of them also wanted global regulation, while recognising that this would be a challenge to achieve.

Is Humanity Capable of Deciding Not To Use a New Technology?

We argue that all major new technologies need continuous broad societal assessment and that this should become the norm as technologies increase their potential to effect major changes in every area of human life and life on this planet. A true precautionary technology assessment process requires concerted effort, courage, and restraint, including considering not using certain applications or strictly limiting their use. One major precedent was the decision to adopt a moratorium on field and commercial releases of genetic use restriction technologies (GURTS) or terminator technology in 2000 at the CBD, reaffirmed in 2006.

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[22] UK Department of Trade and Industry, GM Nation? The Findings of the Public Debate (London, UK, September 2003), http://webarchive.nationalarchives.gov.uk/20100419143353/http:/www.aebc.gov.uk/aebc/reports/gmnationreportfinal.pdf.

[23] UK Department of Trade and Industry, note 22; also see R. Grove-White, P. Macnaghten, S. Mayer, and B. Wynne, Uncertain World: Genetically Modified Organisms, Food and Public Attitudes in Britain (Lancaster, UK: Lancaster University, Centre for the Study of Environmental Change, 1997); R. Grove-White, P. Macnaghten, and B. Wynne, Wising Up: The Public and New Technologies (Lancaster, UK: Lancaster University, Centre for the Study of Environmental Change, 2000), http://www.lancaster.ac.uk/fass/centres/csec/docs/wising_upmac naghten.pdf.

[24] BBSRC, Synthetic Biology Dialogue, Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council (EPSRC), with support of the Department for Business, Innovation and Skills, Sciencewise programme (London, UK, 2010), http://www.bbsrc.ac.uk/documents/1006-synthetic-biology-dialogue-pdf/.

Such moratorium decisions need to be global, and taken at the United Nations level, to be effective.

Questions and Values Related to New GE Techniques and Precaution

The advent of new genetic engineering techniques provides us with another opportunity to discuss technology assessment and advocate for the precautionary principle into the future. If society is to carry out a meaningful assessment of the new genetic engineering techniques, we must decide what questions to ask. Some of these are broad philosophical and ethical questions about the relationship between human beings and other life forms. For example, what is the effect on our values and ethics if we believe that we can freely alter and even eliminate other living things to suit our own essentially short-term interests? By reducing other life forms to digital sequences, do we remove any sense that they have an intrinsic value? Considering how profoundly we depend on ecological systems that we do not yet understand in any detail, is it ethical or scientifically valid to intervene in those systems by intentionally changing or eliminating species and organisms? Two questions asked by participants in the U.K. synbio dialogue are important here: What sort of technology is produced when you are respectful or mindful of nature? What are the consequences of seeing life as nothing more than parts to be assembled?

When it comes to practical questions for the technology assessment process we need, the National Academy of Sciences has published a paper that suggests a number about gene drives:

> *Will applications of gene drives be safe? Will they be effective? Will they have unintended consequences for the environment or public health? Do we know enough to release gene-drive modified organisms into the wild? Is using a gene drive to suppress or eliminate a pest species a good idea? What can scientists do to reduce risks to humans, other organisms, and the environment? How do we decide where gene-drive modified organisms might get released? What should governments do? Who gets to decide?*[25]

The last question is central: All of society should be involved in making these crucial decisions. This must include voices from different cultures, Indigenous Peoples, local communities, and small-scale farmers, women and men who interact with wild ecosystems, save seed, and grow food.

If we are serious about preventing unintended impacts, common sense suggests that we should not release such organisms into the environment while we still know so little about how natural systems work.

The recent finding that hundreds of unintended mutations may have resulted from using the genome editing technique CRISPR/Cas experimentally in mice demonstrates once more how important it is to not rush or be led by assumptions especially where safety is at stake, both for humans and for the environment. Since the extent of such process-derived off-target effects has only recently been demonstrated even though CRISPR/Cas techniques have been around for nearly four years, it is very clear that adequate time is needed to fully understand how these techniques work, with their unintended effects and associated risks.

Furthermore, the positive aspects of a product tend to appear first, while negative impacts emerge later. For example, over the first few years GM herbicide-tolerant crops largely worked as promised for farmers, and only later, as some had predicted, did weed resistance and impacts on human health become apparent. This weed resistance is leading to the

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[25] The National Academies of Sciences (USA), see note 13.

application of ever higher doses and more potent mixes of herbicides, further compounding the impacts on human health. We must break the pattern of learning late lessons from early warnings and instead proactively assess powerful technologies based on reaffirmed precaution.

Further Reflections

Humans have reached a point where we are capable of technical developments that could profoundly change our relationships with other life forms and ecosystems. These could result in a still more human-centred approach that completely blurs the distinctions between species and further commodifies them as general resources to engineer and exploit. Our attempts to do this might have major impacts on evolution that could turn out very differently from our intentions. All this means that we need to pause to consider what we are doing, and whether or not we should do it. If we were to decide to employ very specific gene drives, for example, we would need to carefully and collectively decide what safeguards to put in place. The precautionary principle should be central in discussions about this technology. We need to develop a process that comprehensively embraces the precautionary principle for evaluating all new technologies as they emerge. The full application of precaution would give us the tools, the time, and the space to deliberate in depth and make the wisest possible decisions about humanity's place and role on the planet, rather than simply being swept along wherever new technological developments take us.

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