CONCEPT NOTE

Application of Precautionary Principle to Synthetic Biology Research

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While technological innovation holds the promise of far-reaching benefits for humanity, its unpredictable nature continues to pose risks to our societies. The developments in personal computing and digital interconnectivity, for example, have disrupted the established patterns of social interaction and gave rise to the platform economy and the increased automation of labour. Such developments are notoriously difficult to regulate and, due to their unprecedented and quickly evolving nature, they often outpace or altogether escape the logic of the existing legal frameworks.[2] The question then arises how the governments around the world can cope with the risks involved in rapid technological innovation.

The standard response has been to resort to a form of risk management featuring the application of the precautionary principle to the projects seeking to develop new technologies. The precautionary principle aims to anticipate, prevent or minimize potential risks under conditions of scientific uncertainty.[3] Where the clear scientific evidence is lacking, or where it is impossible to determine the risks resulting from a given activity, the precautionary principle can be used to control the activity in question by managing risks related to certain streams of research, which could involve stopping of certain research projects or ensuring that additional safeguards are implemented in time.

However, as evidenced by the recent rise of many disruptive technologies, the scientific community and policy makers are often taken by surprise and only act when it is already too late. Moreover, the precise formulation and the scope of the precautionary principle have not always been clear. The calls for the application of precautionary principle to technological innovation have resulted in a fair degree of confusion and debate about the precise meaning and desirable scope of precaution. The situation is even more complex in the fields where new scientific discoveries continue to challenge the status quo, while various interest groups push for different regulatory solutions.

In light of the above-mentioned concerns, in this concept note, we review the academic literature dealing with the application of precautionary principle to synthetic biology, one of the quickly developing fields of science. The objective of this concept note is to stimulate further exchanges about the application of the precautionary principle based on the current state of expertise in the field of synthetic biology.[4]

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[2] Julie E. Cohen, "Law for the Platform Economy," *UC Davis Law Review* 51 (2017): 133–204; Lina Khan, "Amazon's Antitrust Paradox," *Yale Law Journal* 126 (2017): 710–805.
[3] Claudia Som, Andreas Koehler, and Lorenz Hilty, "The Precautionary Principle as a Framework for a Sustainable Information Society," *Journal of Business Ethics* 85 (2009): 493–505, https://doi.org/10.1007/s10551-009-0214-x.
[4] We thank Bill Adams, Peter Gluckman and Salvatore Aricò for their insights and comments on the earlier drafts of this note.

CASE STUDY: SYNTHETIC BIOLOGY

Synthetic biology is a growing field of research which consists of design, creation and modification of artificial biological entities and functions. As a cutting-edge area of study, synthetic biology promises unprecedented benefits for our very lives and health. Improved production of drugs and vaccines, advanced mechanisms for personalized medicine, as well as new, programmable drugs and devices for health prevention and treatment have been listed as some of the expected benefits of synthetic biology research.[5]

However, due to the uncertainty and unpredictability surrounding the outcomes of synthetic biology research, the latter may also entail unprecedented and potentially existential risks to humanity. New strains of pathogens can be designed and created, leading to human health risk which might follow from inadvertent or intentional release of such disease agents. The new organisms developed to treat illnesses may also cause adverse effects, infections or unanticipated immune system response in patients. The ability of the biological organisms to reproduce and to evolve presents us with another layer of unpredictability. Fear about such potentially catastrophic scenarios have led academic commentators to call for the application of precautionary principle to synthetic biology research.

LITERATURE REVIEW

The precautionary principle finds application in the regulatory areas characterized by high levels of scientific uncertainty. On the international level, it has mainly been applied in international environmental law. Article 3 of the United Nations Framework Convention on Climate Change (1992) stipulates that 'parties should take precautionary measures to anticipate, prevent, or minimize the causes of climate change and mitigate its adverse effects.' Furthermore, Principle 15 of the Rio Declaration on Environment and Development (1992) states that 'Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.' In accordance with this principle, the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (2000) aims to contribute to ensuring adequate levels of protection with regard to handling, use and safe transfer of living modified organisms resulting from modern biotechnology. The Protocol takes into account the potential adverse effects of such organisms on conservation, biological diversity and human health. The precautionary principle has been used to address the depletion of the Ozone Layer: the Montreal Protocol on Substances that Deplete the Ozone Layer mentions 'taking precautionary measures to control equitably total global emissions of substances that deplete it.'

The precautionary principle has also been applied in the context of food regulation. Multiple states, including Germany and Peru, have issued moratoria which signalled their intention to ban cultivation of GMOs which is based on the uncertainty of available science on the effects of GMOs on public

[5] Presidential Commission and for the Study of Bioethical Issues, "New Directions: The Ethics of Synthetic Biology and Emerging Technologies" (Washington, D.C., 2010).

health and ecosystems.[6] The precautionary principle has also been invoked by the EU in a trade dispute with the US concerning the importation of meat produced with the help of artificial beef growth hormones. The European Commission also issued a communication where it explained that measures based on precautionary principle should be proportional, non-discriminatory, consistent.[7] They should be based on examination of potential costs and benefits, capable of assigning responsibility for producing the scientific evidence for a more comprehensive risk assessment and be subject to review in light of the new scientific data.

The above examples provide us with precedents for the application of precautionary principle in policy areas which might affect human health. However, synthetic biology poses some unique challenges. Wareham and Nardini write that synthetic biology projects entail a risk of catastrophic consequences 'whose severity may exceed that of most ordinary human undertakings.'[8] This is because synthetic biology is a 'threshold technology,' whose outcomes are essentially unpredictable. The uncertainty is aggravated by the fact that creation of artificial life entails working on organisms which are capable of open-ended evolution.[9] Som et al. argue that it is necessary that society can make informed decisions about its willingness to accept technological risk in a situation where scientific certainty about the probability and gravity of risk is lacking.[10]

Fears about unpredictable consequences have led to calls for adoption of precautionary measures. Looking at the widespread mobilization of civil society around this issue, Wareham and Nardini argue that citizens appear to want the precautionary principle to regulate synthetic biology, which vests its application with an additional degree of democratic legitimacy.[11] They advocate for an evidence-harm proportionality rule: 'if the potential harm of an activity is greater, stronger evidence that the harm will not occur is required in order for the activity to take place. Or as a corollary: if the potential harm of an activity is greater, weaker evidence that the harm will take place is required in order to prevent the activity.'[12] Seen in this way, the precautionary principle can be seen as a limitation on the level of acceptable risk.

A weaker formulation of the precautionary principle would require the potential risks resulting from an activity to be irreversible. According to this formulation, the cost of precautionary action could not outbalance the potential benefits of continuing technological development. Such way of framing the argument relates to the principle of intergenerational justice in a situation where a large number of people living in the future would be affected by the decisions taken by people acting in the present.[13] The latter principle is relevant in the context of synthetic biology: future generations will

[6] Jose-Felix Pinto-Bazurco, "The Precautionary Principle" (International Institute for Sustainable Development, 2020), https://www.iisd.org/system/files/2020-10/still-one-earth-precautionary-principle.pdf.
[7] European Commission, 'Communication from the Commission on the precautionary principle' COM/2000/0001.
[8] Christopher Wareham and Cecilia Nardini, "Policy on Synthetic Biology: Deliberation, Probability, and the Precautionary Paradox," *Bioethics* 29, no. 2 (2015): 118–25.
[9] M. Bedau and E. Parke, eds., *The Ethics of Protocells* (Cambridge, Massachusetts: MIT Press, 2009).
[10] Som, Koehler, and Hilty, "The Precautionary Principle as a Framework for a Sustainable Information Society."
[11] Wareham and Nardini, "Policy on Synthetic Biology: Deliberation, Probability, and the Precautionary Paradox."
[12] Ibid.
[13] Som, Koehler, and Hilty, "The Precautionary Principle as a Framework for a Sustainable Information Society."

potentially have to live with the consequences of decisions which cannot be reversed or cope with developments which can no longer be controlled.

In a stronger formulation, precautionary principle could be used to block research projects based on a mere possibility of a project leading to harmful consequences. In this view, speculative measures should be taken whenever there is any potential evidence of a risk.[14] For example, some members of the civil society have proposed that synthetic microbes should be treated as 'dangerous until proven harmless.'[15] Such approach is based on an argument that it is better to err on the side of caution when dealing with technologies which may pose existential risks to humanity.

The stronger formulation of the precautionary principle has attracted criticism in the academia. Sunstein criticizes the precautionary principle for only taking into account the possible harmful consequences of an action and for disregarding potential benefits.[16] Wareham and Nardini write of a situation where the value of potential harm is so high, that even a slightest probability of potential harm is sufficient to trigger the precautionary action and, for example, suspend a given research activity.[17] However, failing to work on a specific project can also cause harm, which results in a 'precautionary paradox.' This paradox is particularly relevant in an area of research which could potentially entail existential risks for humanity.

Sandin et al. review and respond to the charges levelled against the precautionary principle.[18] They defend the precautionary principle by arguing that it is no more ill-defined, ideological and unscientific than any other decision principles and that it needs to be made precise through further elaboration and practice. They propose establishing a threshold requirement for probability of the harm actually occurring: the degree of scientific evidence required to trigger precaution could be specified alongside a *de minimis* rule and, thus, allow certain projects to continue.[19] Wareham and Nardini comment that, in many situations, it would simply be impossible to say whether probabilities of harm fall below or above the threshold of tolerable risk.[20] Therefore, representative focus groups could be asked questions by an investigator appointed by a relevant authority and engage in deliberations about the lower boundaries of probability.[21] In case of participants arriving at different thresholds, thresholds could be aggregated and other conflict resolution methods could be employed.

While discussing the social and ethical implications of creation of artificial cells, Bedau and Triant write that the most challenging instances of the use of precautionary principle concern the 'decisions

[14] Som, Koehler, and Hilty.
[15] Action Group on Erosion, Technology and Concentration (ETC), "Extreme Genetic Engineering: An Introduction to Synthetic Biology" (Motreal: ETC, 2012).
[16] Cass R. Sunstein, "Beyond the Precautionary Principle," *University of Pennsylvania Law Review* 151, no. 3 (2003): 1003–58.
[17] Wareham and Nardini, "Policy on Synthetic Biology: Deliberation, Probability, and the Precautionary Paradox."
[18] Per Sandin et al., "Five Charges against the Precautionary Principle," *Journal of Risk Research* 5, no. 4 (2001): 287–99, https://doi.org/10.1080/13669870110073729.
[19] Ibid.
[20] Wareham and Nardini, "Policy on Synthetic Biology: Deliberation, Probability, and the Precautionary Paradox."
[21] Ibid.

in the dark,' where the empirical evidence might be inconclusive.[22] The unprecedented nature of such innovations makes it extremely difficult to predict their consequences, with the statistical analysis of probabilities being of little use: 'it will be often impossible to ascertain the probability of an action causing a catastrophe with anything like a requisite precision.'[23] In such context, any exercise in identification of risk threshold may be deemed arbitrary. To address the difficulty of deciding in the dark, Steel proposes a schema for the precautionary principle based upon the consistency and proportionality in face of potential risks.[24] In this reading, different iterations of the precautionary principle should consider the degree of knowledge that an activity would lead to harm, the magnitude of the potential harm and the counter-scenarios which could arise from banning a given activity. Bedau and Triant propose a set of virtues to guide policy action and argue that balancing courage with caution would preserve the utility of the precautionary principle while avoiding the loss of potential benefits through inaction.[25]

Another proposed solution to making 'decisions in the dark' is to resort to the Bayesian approaches to probability.[26] According to the Bayesian framework, the probability assigned to an event corresponds to the degree of belief that a rational agent should hold about the occurrence of the event.[27] The latter should follow the rules of probability calculus with regard to mutually exclusive outcomes. Objective Bayesianism, which has been presented as particularly well suited to address synthetic biology research,[28] would follow the same rules and include an additional requirement of equivocation.[29] According to the requirement of equivocation, the beliefs of a rational agent should be as close as possible to an ideal balance of probability. The situation of ignorance should not lead a rational actor to assign a higher probability to one of the possible outcomes. Seen in this way, the rational assignment of probabilities would be least committed to all possible alternatives and, thus, equivocal. To illustrate the application of objective Bayesianism to synthetic biology, Wareham and Nardini propose to think about the hypothetical scenario of a research project which aims to prevent a naturally occurring pandemic, while also involving the creation of a potentially harmful synthetic pathogen.[30] A precise risk threshold about possible scenarios could be set through public deliberation. Experts would then be consulted to determine whether probability range of beneficial and harmful outcomes are below or above the threshold. If there exists no prior relevant knowledge to draw from or where there is no certainty whether a given activity is below or above the threshold, probability of 50% should be assigned to the likelihood of a harmful outcome, thus leading to the suspension of the project. Due to the requirement of equivocation, objective Bayesianism is therefore the most risk-averse approach in a technical sense, as it assigns the highest rational degree of belief to potential harms.[31]

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[22] M. Bedau and M. Triant, "Social and Ethical Implications of Creating Artificial Cells," in *The Ethics of Protocells*, ed. M. Bedau and E. Parke (Cambridge: MIT Press, 2009), 31–48.
[23] Ibid.
[24] D. Steel, *Philosophy and the Precautionary Principle: Science, Evidence, and Environmental Policy* (Cambridge: Cambridge University Press, 2014).
[25] Bedau and Triant, "Social and Ethical Implications of Creating Artificial Cells."
[26] Wareham and Nardini, "Policy on Synthetic Biology: Deliberation, Probability, and the Precautionary Paradox."
[27] Colin Howson and Peter Urbach, *Scientific Reasoning: The Bayesian Approach* (Chicago: Open Court, 2005).
[28] Wareham and Nardini, "Policy on Synthetic Biology: Deliberation, Probability, and the Precautionary Paradox."
[29] Jon Wiliamson, *In Defence of Objective Bayesianism* (Oxford: Oxford University Press, 2010).
[30] Wareham and Nardini, "Policy on Synthetic Biology: Deliberation, Probability, and the Precautionary Paradox."
[31] Wiliamson, *In Defence of Objective Bayesianism*.

QUESTIONS ABOUT THE FUTURE OF REGULATION

While the academic literature offers an array of considerations regarding the application of precautionary principle to synthetic biology, it also leaves us with some important questions.

The first set of questions concerns where and how to regulate the quickly developing technology. Traditionally, synthetic biology has been regulated at the national level and has been subject to different regulatory standards and ethical sensibilities. Holm argues that synthetic biology research and applications will be subject to different regulatory agencies, therefore making it difficult to ensure consistency across different policy contexts.[32] The role of the government is to navigate the different fora in order to find appropriate regulatory solutions. The following questions arise: what kind of regulatory standards should apply to synthetic biology research? How can we ensure that governments are furnished the most up-to-date scientific data in a quickly evolving decision-making context?

Linked to the above is the question of the global distribution of costs and benefits of synthetic biology research. Depending on the context, different values might be assigned to the costs of action or inaction on a given topic. Businesses may be tempted by the vision of unprecedented returns; the industry might promise solution of global problems through innovation and deflectthe public attention from regulatory and geopolitical solutions while ignoring the difficult-to-calculate risks. States may also take different regulatory approaches towards synthetic biology depending on the size of their industry and the strength of their human rights, health, or environmental protection safeguards. This leaves us with another question: what are the geopolitical implications of synthetic biology research?

Finally, questions arise with regard to the representation and inclusiveness of the synthetic biology policy discourse. While the scientific community offers a variety of opinions, other voices must also be brought to the table. The indigenous communities, whose traditional practices may be affected by synthetic biology research, should be represented in subsequent discussions. We end this note with the following questions which point to the need for further interdisciplinary and intercommunity exchanges: how to ensure representation of different voices in the synthetic biology policy discourse? How to make sure that the costs of innovation are not borne by marginalized groups?

[32] Sune Holm, "Deciding in the Dark: The Precautionary Principle and the Regulation of Synthetic Biology," *Biology, Ethics, Policy & Environment,* 22, no. 1 (2019): 61–71, https://doi.org/10.1080/21550085.2019.1581419.