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New Genetically Modified Organisms (GMOs): Towards a "scientific precautionary principle"

Giuseppe Longo[a*]

[a] *Centre Cavaillès, CNRS and Ecole Normale Supérieure, Paris, France*

***Corresponding author:** Giuseppe Longo, Email: *giuseppe.longo@ens.fr*

Abstract

To the ordinary precautionary principle, we should add a more precise "scientific precautionary principle". In short, we cannot act on nature based on 'dogmas' that are either manifestly false or are implicitly adopting an uncritical way of thinking. Science is the invention of a new way of thinking, of new theoretical frameworks, starting from a critical review of the principles mobilized, which are themselves well explained. Without this, technoscience, in all its power, becomes a nightmare, as it is totally unsuited to make us live in an ecosystem with all its complexity. The case of New Genetic Technologies, whose application to agriculture is under discussion in Europe, is paradigmatic and urgent.

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In recent months, a relentless campaign, with the help of many lobbyists, is moving through the European Parliament and Commission the NGT (New Genetic Technologies) as an eligible variant to grow GMOs (Genetically Modified Organisms) in Europe. The *European Network of Scientists for Social and Environmental Responsibility* (ENSSER: https://ensser.org/, see also the commitment of the AAGT : https://generation-thunberg.org/accueil), with other non-governmental organizations, is conducting a difficult scientific and political battle against these new products.

The motivations for this new commercialization refer to the so-called «naturalness» of these powerful genomics techniques, called CRISPR-Cas9, which are based on an important scientific discovery, about twenty years ago, on how bacteria may affect the DNA of certain viruses. Now, it is one thing to identify the processes that take place in very complex evolutionary contexts, refined by a long biological history, but it is another thing to use them outside of well-confined laboratories. In these laboratories, CRISPR has been shown to be very useful for DNA and RNA analyses, which have allowed us to understand its great power as well as its limitations (see references below and in (Longo 2021)). Admittedly, these tools are anything except "very accurate". Already in the case of GMOs so far banned

in Europe, the pesticides to which they are resistant or the toxins they produce attack many symbionts, well beyond the target parasite, thus disrupting the humus, i.e., the living layer of soil essential to fertility. Indeed, these molecules act on almost everything that is alive, just with lower probabilities than on the target parasite. The same lack of precision and the impossibility of perfect "steering" of the plant in the ecosystem also concerns these NGTs. However, it is claimed that they can allow us to "perfectly control" the development and insertion into the ecosystem of the plants concerned. This conclusion is based on erroneous "scientific" dogmas—points 1 and 2 below—and without accepting a debate on the failures of existing GMOs, which are also grounded on the same dogmas, see (Kranthi & Stone 2020). For example, no mention is made of the side effects of "BT cotton" in India (Gutierrez, Herren, & Kenmore 2020), of the loss of diversity due to GMOs about maize diversity in Mexico and monocultures (Landry 2015; Rodríguez Mega 2018).

Faced with the abuse of these powerful but poorly understood techniques, presented within a nonsensical, dogmatic frame from the scientific point of view, it is necessary to lay down a "scientific precautionary principle", which should accompany and better specify the "precautionary principle" that is often mentioned. In short: one cannot act on nature on the basis of a "theoretical frame" or, in this case, of "dogmas", that are manifestly false and very often recognized as false even by their very promoters, usually in private (see below for an explicit, late acknowledgement). This behavior is a novelty in science, and it falls outside of any scientific ethics.

The application of GMOs and NGT we are talking about is based on two major dogmas of Molecular Biology that justify the application of the NGT in the ecosystems:

1 - the Central Dogma of Molecular Biology (synthetically: the "information" contained in DNA is "complete" as to the development and evolution of organisms (Crick 1970)—or even "development is entirely written in DNA" as in a computer program). Typically, any contribution of epigenetics to this information is excluded.

2 – the dogma that macromolecular interactions are "exact", (stereo-)specific, as they say, "key-lock correspondence" or "hand-glove"... as this would be "necessary to transmit genetic information", citing (Monod 1970). This makes the cell, even the organism, a "Cartesian mechanism" or "a Boolean algebra", according to the latter.

The second dogma is not less important or less obviously false than the first. For decades, physico-chemists have treated these interactions statistically—macromolecules have enormous oscillations, move in a Brownian stream and almost all their chemical affinities depend also on their context. A marginalized minority in biology has been defending this evidence since 1983 (see for an overview (Paldi 2020)), further developed by a more echoed article on this subject in 2002 (Elowitz *et al.* 2002). The two dogmas are at the basis of a mechanistic (Cartesian) vision of the living, as particularly emphasized by Francis Bacon (1561–1626, cited since the 1930s by the promoters of genetic engineering): in this perspective animals and plants must be considered and treated as machines... We may reprogram them at leisure by "editing" the "selfish genes" that completely encode them, claim the promoters of geno-centrism still today (Dawkins 2016). For them, everything is information, encoded in the genes, modifiable at leisure—and it may be "edited", exactly, like an alphabetic text, letter by letter.

It is amazing to hear, from private conversation or secondary publications, the proponents of these dogmas recognize that they are false. E. Fox-Keller closely analyzed this phenomenon. In particular, she quoted Philip Ball, a "former editor" of the journal *Nature* who recognized "the misleading nature" of these dogmas, despite their use in any popularization and in most academic textbooks. These "'misleading' narratives are routinely perpetuated in the teaching of Molecular Biology, indeed in so much of the technical, the lay, and even the philosophical literature", wrote Ball, quoted in (Fox-Keller 2020), who also offered a historical perspective in (Fox-Keller 2003) (for theoretical alternatives to geno-centrism, see (Soto *et al.* 2016)). Indeed, these narratives are at the core of all kinds of promises in genetic technologies and... of the sale of shares on the stock market of the start-ups that work on them.

Based on these dogmas, it can be stated that we have the "power to control evolution", according to the title (and the content) of the 2017 book by J. Doudna (J. Doudna and E. Charpentier, were awarded the 2020 Nobel Prize for the remarkable technique they developed). CRISPR-Cas9, she writes, may reprogram the genome by acting on the DNA "exactly", by "editing"

it, "as with scissors"... while in laboratories these same authors act on large numbers of cells, choosing the cells where the process has worked (cherry-picking) (Bock *et al.* 2022). Gene knockouts, which has been practiced for decades, may not work (Smits *et al.* 2019); CRISPR-Cas9 modifications designed to suppress gene function may fail, and damaged genes may continue to produce proteins (many of which are still functional), just as there are collateral and/or unpredictable effects (Burgio & Teboul 2020), as well as editing-resistance (Mehta *et al.* 2019). The process instability is particularly evident when CRISPR-Cas9 is applied to animal models (Papathanasiou *et al.* 2021). It is therefore quite possible that after a very large number of transgenic manipulations and experiments of many different techniques, the few temporary successes in implantation in the fields of existing GMOs are *less due to the relevance of the genetic manipulations than they are to the great resilience of living organisms*. But this resilience has limits: the transformation of humus into sand in a few years is one of the most serious consequences of existing techniques (Bizzarri 2012)—but not the only one (see the case of Teosinte: uncontrolled diffusion in the fields of this wild maize, inedible, would correlate with an "adaptive crop-to-wild introgression of transgenic maize"—the "noxious weed" (Le Corre *et al.* 2020)).

The book by J. Doudna is a paradigm of the geno-centered approach, based on the two dogmas cited above (the first explicitly, the second implicitly) and on the marketing of NGTs, rich in promises without criticism, without any reflection on the limits and failures of existing GMOs. Application of these old techniques should have solved the problem of hunger in the world (as it was said in 2000), and similarly we should be able to do so today by using NGTs, while adjusting life to the changing ecosystem. This is claimed with no reference to the limits of these new techniques, which are the result of an immensely complex technicality that intervenes on the living on the basis of the same dogmatic imaginary as the old GMOs. Science, on the contrary, is the invention of a new way of thinking from a critical perspective of the principles mobilized, themselves well (and honestly) displayed. Without this, techno-science, in all its power, becomes a "nightmare", like the one we are experiencing as a result of the limitless extractivist engineering techniques that have changed the climate. I am referring here to the role of fossil fuel extraction and its transformation through innovative and very powerful techniques and their a-critical use, for more than a century, without a 'theoretical' unified thinking of the Earth and its atmosphere (Longo 2023).

The life sciences can and must use these NGT in laboratories, including this new and formidable CRISPR-Cas9 technique, and perform genetic manipulations in well-isolated bio-reactors (with enormous vigilance against possible leaks). The production of insulin by genetically modified bacteria is *the* great success of a now mature, 50-years old technique. Insulin, an inert product, is then released from the bio-reactors. Conversely, the insertion of organisms resulting from genetic manipulations into the complexity of ecosystems is a serious error. Both the set of all induced mutations on plants and the side effects on the context, such as the humus, are a priori unpredictable, like the effects of traditional GMOs. More generally, the networks of changing interactions that characterizes the living is anything but a system on which one can think of acting as with a "Swiss army knife". These methods have nothing to do with the patient co-evolution of top-down human techniques (grafts, hybridizations, etc.). Of course, even by these traditional techniques we can do damage: when we create huge monocultures of perfect apples, all identical to Snow White's apple, we have lost the scientific sense of the role of diversity in the resilience and, thus, evolution of the living.

To summarize, these techniques of genetic engineering are without scientific support and are not adapted to help us live in an ecosystem, which we must also or first understand. And we also should acknowledge the scientific limits of these powerful techniques, such as the following: a false or incomplete theoretical framework; often unattainable genetic targets; off-target effects; previous failures in other forms of genetic manipulation, and finally, the inherent unpredictability of many phenotypic and ecosystem consequences—for a review and references, see (Longo 2021).

In this context, accepting GMOs, based on these NGTs, which "do not produce more than 20 mutations" (as proposed in the new European regulation (Nature Plants Editorial Board 2023; ENSSER 2023) is a nonsense: in no case we can predict the exact nature and number of mutations that will be induced by these

techniques, even less their phenotypic and ecosystem consequences.

The argument of the "20 mutations" is based on the observation that a larger number of mutations is very unlikely to be produced by evolutionary chance (Nature Plants Editorial Board 2023). This argument does not imply that the induced mutations, below 20, would be "natural" (the flows in Logic and the abuse of the "differential method" were the first observation of this author, a mathematician, when reading texts of "dogmatic" molecular biology (Longo & Tendero 2007)); it only makes it more difficult to trace artificially induced mutations, against any obligation of transparency. Further, we have just come out of a pandemic where a single mutation, N439K, in SARS-CoV-2, has profoundly modified, and in a largely unpredictable way, the pathological effects of the virus, since it "enhances the binding affinity for the ACE2 receptor and reduces the neutralizing activity of some monoclonal antibodies (mAbs) and polyclonal antibodies present in sera from people who have recovered from infection" (Harvey *et al.* 2021).

Acting on the environment on these bases is equivalent to entrusting to the 11th century great astronomers with missiles capable of reaching Mars. These astronomers were remarkable observers and mathematicians, but they were working within the Ptolemaic, geo-centered, theoretical frame. Thus, they were wasting a lot of time in drawing epicycles, with little predictive effectiveness, while working in... Astrology, that is at making *promises* and *predictions* (Longo & Mossio 2020)— not dissimilar to the 2003 promise to wipe cancer off the face of the Earth by 2015 through gene therapies as claimed by (von Eschenbach 2003), then president of the National Cancer Institute. Not only those missiles would never have reached Mars, but they would have fallen on a nearby city or exploded for excessive acceleration because their preparation would not have taken into account the rotation of the Earth. In addition to asking for caution (the traditional "precautionary principle"), we must insist on calling attention on the false theoretical framework of the old and new genetic technologies mentioned above and the duty of *scientific precaution* not to implement them in the Earth's ecosystem. This is done in some debates, but far too rarely (for some documents on the ongoing battle at European level, in which ENSSER is participating, see: https://ensser.org and www.di.ens.fr/users/longo/files/NGT-public-linksJuly5-2023.zip).

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