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Subject : report on « genome edition »

Dear Comitee members,

It is in your mission to discuss the ethical issues of « genome edition » in a very wide range of aspects. You organized a roundtable at Brussel on October 16th, to which we had the opportunity to participate and we thank you for that. We wanted to submit a written contribution to you in order to say more things, but also to support and argue them.

Below, we discuss the status and origin of the mission (Section 1), then the words used (Section 2). The hidden intention behind the distorted words (« cut and paste », « genome edition », « New breeding technique », « resistant and tolerant crops ») helps understanding the political and technical issues. We also discuss what related techniques are hidden behind the main techniques and what their denial reveals (Section 3). We give three case studies (Section 4), discuss detectability, traceability and labeling (Section 5), recall the claims and lies in the past (Section 6), come back to more ancient claims about genetic and especially eugenics (Section 7) and then we conclude (Section 8).

1) The mission

1.1) Who gave the mission?

The mission was given by the *Research and Innovation* Department of the European commission.

> « This Commission department is responsible for EU policy on research, science and innovation, with a view to help create growth and jobs and tackle our biggest societal challenges. »[1].

We believe innovation is devoted to pursuing the race as it is (infinite growth and just-in-time management). We always go further and faster but we know less and less where we go. It stems an uncomfortable feeling of being managed and not being able to decide of our future (liquid society of Z. Bauman). Authorities want us to get adapted to their Progress. Tackling « our biggest societal challenges » must not be managing « our biggest societal challenges » by adapting us to the techniques, science and economy developed. Politics is not reduced to management and the increasing complexity of techniques in our world could rule citizens out of Politics. Indeed, this agenda of innovation, dodging, and management is not our and we prefer political commitment. Would any of the proponents of Innovation defend to prohibit anything forever? No. Their mission is to ease the scientific (and economic) growth. We do not trust in infinite growth. Our opinion, though it is rather natural (how can a finite system grow infinitely?), is never raised … in the classical medias nor in the progressists speeches.

1.2) Ethicists

To be honest, we do not trust political authorities nor regulation authorities (we will depict an example). The only possibility is to settle a true debate where words will be analyzed, techniques will be described even in some of their details. Only then a position can be claimed.
So, ethicists are our best hope. Yet, the title or qualification does not guarantee anything.

1 https://ec.europa.eu/info/departments/research-and-innovation_en

For instance, Peter Singer, an *utilitarian* ethicist states[2]

> « If we compare a severely defective human infant with a nonhuman animal, a dog or a pig, for example, we will often find the nonhuman to have superior capacities, both actual and potential, for rationality, self-consciousness, communication and anything else that can plausibly be considered morally significant ».

In 1979 Singer wrote[3]:

> « Human babies are not born self-aware, or capable of grasping that they exist over time. They are not persons », therefore, « the life of a newborn is of less value than the life of a pig, a dog, or a chimpanzee. ».

The same, still evaluating in an *utilitarian* way the lives of both animals and "defective infants", writes[4]:

> « the fact that a being is a human being, in the sense of a member of the species *Homo sapiens*, is not relevant to the wrongness of killing it; it is, rather, characteristics like rationality, autonomy and self-consciousness that make a difference. Defective infants lack these characteristics. Killing them, therefore, cannot be equated with killing normal human beings, or any other self-conscious beings. »

Since he is convinced to be able to evaluate the capacities, he is then able to compare and measure lives. This is typical of the utilitarian philosophy.
But there are also some marvellous philosophers whom we enjoy, such as H. Arendt. G. Anders, I. Illich, L. Mumford, G. Orwell, C. Lasch ...

2) Some words
Definitely, before making statements, one must think and organize one's thoughts. Even before, one must observe, read and hear the various positions.
But in this process, mixing-up ideas is very much aided by the ambiant mixing-up of words. So, we will devote a large part of our report to discussing words.

2.1) Cut and paste
A very good article was written in *The Conversation*[5] so as to criticize the saying of « cut and paste » in biotechnology. The author, Elinor Hortle, is Research Fellow at the University of Sydney. This article complements some of the arguments below.

2.1.1) Behind computers
The metaphor of the cut and paste from computer science is misleading. Some texts cannot be taken out of a pdf file (if graphical). When you copy a text from an html "window", it is copied in a local memory (in a given format) and if you paste it into a doc file, it must be transformed into another format. That is the reason why it does not work all the time. The spaces, types of fonts, footnotes, do not always remain. And since, in our societies, computer science is associated to the will to go fast, always faster but without knowing where we go, we do not take time to understand why. And we propagate some errors that may interact. Provided we manage them, we may believe we are safe. For the time being. What about the others?

All the same is true with genetic modifications. Bo Huang, a biophysicist at the University of California, San Francisco says « People just don't have the time to characterize some of the very basic parameters of the system. […] There is a mentality that as long as it works, we don't have to

2 Sanctity of Life or Quality of Life, *Pediatrics*, July 1983, 129
3 Peter Singer, *Practical Ethics*, 1st ed. (Cambridge: Cambridge University Press, 1979), 122–23
4 Peter Singer, *Practical Ethics*. 2nd edition, Cambridge, 1993, pp. 175
5 https://theconversation.com/why-the-molecular-scissors-metaphor-for-understanding-crispr-is-misleading-119812

understand how or why it works. »[6]. That means that researchers occasionally run up against glitches. But looking after errors takes time and Progress has no time left. Here we criticize not only the companies, the capitalism but also the public research, and even the society and its dodging.

We recommand the GIET's analysis for deeper analysis in biotechnology[7]. Very roughly, they argue that genetically changing some species at a velocity that prohibits genetic coevolution forces the whole system and might trigger nonlinear amplifications that can act as a chaotic system!

2.1.2) Biology 1 (genotype/phenotype)
Even though it will be obvious, we want to remind the reader that the link between the genotype and the phenotype is still rather unknown and it is one of the big biological challenges. Many steps are not known such as the correlations between a phenotype and single nucleotide mutation, topologically associated domain, epigenetics and epitranscriptomics. We will prove that even if they were under control, the ethical question would remain and it will be one of our main points.

2.1.3) Make up a gene (before insert)
One is often explained in a patronizing way that scientists cut a gene in the bacteria and paste it into the corn. Behind such a statement, are hidden various realities and also various related/associated techniques that we will prove to be relevant for any definition of GMO, any assessment, any regulation, any labeling and any naming (see Sections 3.1, 3.2).

First, one *must* change the promoter (very first part of the gene in the 70s' view of molecular biology) and insert a promoter that would be strong so as to be sure it will be efficace. An article proved that the promoter associated to a gene, inserted in a plasmid, was so efficient that the whole plasmid was read two or three times, ignoring the terminator (endpoint of the gene)! So this promoter is so efficient that it does not do only what scientists say it does.
Then one must change the enhancer which is the meta promoter that controls various genes associated to the same function and sometimes far away in the linear sequence[8].
Then one must optimize the terminator.
Then again one must change some codons, even though they are associated to the right amino acids, but bacterial and plant species have different customs in translation systems, about which we know very little.
Last, even having done all this, the Syngenta corn did not "work" because the Bt protein was not produced. So the company had to insert a truncated coding sequence of the gene so as to have the already active Bt protein (it usually gets active in the gut of lepidoptera)[9].
And we are said it is a simple « cut and paste »?
We stop here at the level of the GM cell and keep the regeneration of the whole plant for below (Sec. 3.2).

2.1.4) Epigenetics and beyond
As is rather well known by specialists, the genetic information is not depending only on the genomes of nucleus and plasts. It depends also on the epigenomes, taken here as covering both epigenome and epitranscriptome (also called RNA epigenome). To what extent GMO are checked for (epi)genetic modification? The current dossiers for risk evaluation do not include any information about epigenomes, which are indeed currently recognized to be transmitted to the offspring for several generations.
Alternative splicing varies, not only between species but also among cultivars. So a same gene will not provide the same protein in two different species.

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6 Ledford 2015a. Crispr, the Disruptor. *Nature* 2015 Jun 4;522(7554):20-4. doi: 10.1038/522020a.
7 http://www.evaglo.net/
8 LA. Pennacchio *et al.* Enhancers: five essential questions. *Nature Reviews. Genetics.* **14** (4): 288–95. (April 2013). doi:10.1038/nrg3458.
9 M. Vaeck *et al*. *Nature* **volume 328**, pages33–37 (1987) https://www.nature.com/articles/328033a0

Would it be possible that there be something more than this epigenetics? Something like pangenomes that would interact? The pangenome notion tells us that the species variability does not allow us to accurately predict the effect of genetic or epigenetics changes inside a genome. As reported by Jeffrey Sanders (Pioneer); the distance between two corn cultivars is the same as between human and chimpanzee. This is not science-fiction since we do know there are chaperones proteins that are different according to the species, genus or kingdom. Even if the linear formulas of proteins are the same, despite the variability of introns/exons, the chaperones proteins decide of the folding and so of active sites of the folded protein. So the “cut and paste” metaphor is merely stupid since a given gene may provide very different functionalities[10].

2.1.5) Small is large

Let us take an example. On August 1st 2016, the Belgian Authority (Kelly Lardinois from SBB) was asked by a public biotechnology laboratory (VIB) whether Crisperized corn should be regulated. The « genetic modification » (stated like this!) will be discussed below, but it had in one case a deletion of *one* basis pair (should it work the way the VIB wanted !).
So as to make understand (and smile) the reader, we assume we have an alphabet of 26 letters in which we declaim the sentence:

To be or not to be.

Should we switch the encoding of the letters, the A would get B, the B would get C and so on. The Shakespeare's sentence would be modified to?

Up cf ps opu up cf.

The whole meaning is totally (and entirely) modified. Concerning genetics, let us assume the basis sequence is

.GGT.ACT.TTG.ATA.ACG

If, similarly, we take off the first basis, we shift the frame of the coding sequence. It would become (the first G is deleted):

_.GTA.CTT.TGA.TAA.CG[11] …

So a single deletion shifts the whole reading frame and the protein will be *totally modified* since it changes the topologically associated domain (TAD) in a nucleus as reported.

Similarly, the Agouti gene contributes to the colouring of the leopard's coat. It was enough for a C (=cytosine) base to be replaced at position 333 by an A (=adenine) base in a UGC codon to transform this codon into a UGA[12]. Such a codon stops transcription (STOP codon). This replacement of a single base removes 25 amino acids from the Agouti protein and explains an important phenotypic property (the panther is black for a single replaced base). So what is a small change?

It should be noted that a simple change (insertion, deletion or replacement) can have significant changes, even if it is apparently small.

10 Through alternative splicing, 38,016 variant fruit fly proteins can be made by a single gene. Schmucker D, *et al.* Drosophila Dscam is an axon guidance receptor exhibiting extraordinary molecular diversity. *Cell.* (2000) Jun 9;101(6):671-684. https://doi.org/10.1016/S0092-8674(00)80878-8

11 The very specific example given make appear a STOP codon (TAA) that ends the synthesis of the protein. Many other things may happen. For such an effect with CRISPR, see Ran FA, Hsu PD, Wright J, *et al.* Genome engineering using the CRISPR-Cas9 system. *Nat Protoc.* 2013;8:2281–2308. DOI: 10.1038/nprot.2013.143.

12 Schneider A, *et al.* (2012) How the Leopard Hides Its Spots: *ASIP* Mutations and Melanism in Wild Cats. *PLoS ONE* 7(12): e50386. https://doi.org/10.1371/journal.pone.0050386

The official page describing the Belgian corn's modification[13] speaks of "frameshift mutation". Scientists claim the gene is then "knocked-out" (KO) and, indeed the protein will no longer be produced[14]. But a very different one will be produced instead. Nobody is able to predict its function. In addition, numerous "moonlighting proteins", i.e. with several functions according to the cellular cycle, can be affected by intended or unintended changes. A small deletion of one, two or four bp can be more drastic than the deletion of three bp (that would change « only » one aminoacid) since its changes are non-local. Many laboratories have reported of alternate downstream start codons, active truncated variants, alternative splicing, or in frame exon-skipping that interfere with the complete knockout phenotype depending on the location of the indel[15].
This is not even considered by the scientists nor by the Belgian Authority which takes for granted that if a protein is not produced (but another one is produced with similar or different functions!), one may consider that only the "initial" gene was knocked out. The possible non-standard protein synthesis is not discussed and very likely unseen. Can we deduce there is no risk?
Let us add that the other genetic modifications of the project aimed at modifying 1,271 bp; 1 bp (twice) and 119 bp and that these numbers are no more a multiple of 3.
This is clearly stated in an article that « a systematic understanding of the efficiency of protein elimination has been lacking. »[16]. More precisely, the scientists « observed residual protein expression for about one third of the quantified targets » and according to the way the gene was knocked-out, many of the proteins remained partially functional (because for instance only the internal part of the conformed protein was changed or the modified exons were skipped). Exon's skippings may occur too[17]. They are playing the Casino to discover the secret law of Life … to modify it and even write it, which makes them feel like gods. These Strangelove Doctor's studies mix up the laboratory and the world. Belinda Martineau, was the scientist at Calgene who made up the very first GMO FLAVR SAVR. She says[18]:

> *when science moves out of the lab and onto the plates of consumers we must be more cautious about it.*

Dr Larry Gilberston, molecular biologist for Bayer Life Science company also said[19]:

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13 https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/crispr_mais_bijlage_11_snif_0.pdf

14 A good description and even some critics may be found in https://www.genome.gov/about-genomics/fact-sheets/Knockout-Mice-Fact-Sheet

15 Miao J, *et al.* Characterization of an N-terminal non-core domain of RAG1 gene disrupted Syrian Hamster model generated by CRISPR Cas9. Viruses. (2018) 10:243. DOI: 10.3390/v10050243
Lalonde S, *et al.* Frameshift indels introduced by genome editing can lead to in-frame exon skipping. *PLoS One*. (2017) 12:e0178700. DOI: 10.1371/journal.pone.0178700
Kapahnke M, Banning A, Tikkanen R. Random splicing of several exonscaused by a single base change in the target exon of CRISPR/Cas9 mediated gene knockout. *Cells.* (2016) 5:45. DOI: 10.3390/cells5040045.
Mou H, Smith JL, Peng L, *et al.* CRISPR/Cas9-mediated genome editinginduces exon skipping by alternative splicing or exon deletion. *Genome Biol.* (2017) 18:108. DOI: 10.1186/s13059-017-1237-8.
Makino S, Fukumura R, Gondo Y. Illegitimate translation causes unexpected gene expression from on-target out-of-frame alleles created by CRISPR-Cas9. *Sci Rep.* (2016) 6:39608. DOI: 10.1038/srep39608.
Smits AH, *et al.* Biological plasticity rescues target activity in CRISPR knock outs. *Nat Methods.* (2019) 16:1087–1093. DOI:10.1038/s41592-019-0614-5.

16 Smits, A.H., Ziebell, F., Joberty, G. *et al.* Biological plasticity rescues target activity in CRISPR knock outs. *Nat Methods* **16,** 1087–1093 (2019) doi:10.1038/s41592-019-0614-5 https://www.nature.com/articles/s41592-019-0614-5

17 Sharpe, J.J. & Cooper, T.A. (2017) Unexpected consequences: exon skipping caused by CRISPR-generated mutations. *Genome Biology*, 18(1): 109 ; Tuladhar, R. *et al.* (2019) CRISPR-Cas9-based mutagenesis frequently provokes on-target mRNA misregulation. Nature Communications, 10(1): 4056. https://www.nature.com/articles/s41467-019-12028-5 ; Mou, H. *et al.* (2017) CRISPR/Cas9-mediated genome editing induces exon skipping by alternative splicing or exon deletion. *Genome biology*, 18(1): 108. https://genomebiology.biomedcentral.com/articles/10.1186/s13059-017-1237-8

18 https://non-gmoreport.com/articles/march2014/scientist-journey-from-gmo-believer-to-skeptic.php

19 https://www.euractiv.com/section/agriculture-food/video/bayer-scientist-regulation-and-risk-assessment-must-evolve-with-technology/

> *there's no intrinsic difference in the risk between [GM and « NBT »] […] whether it's classical breeding, random mutagenesis, or these new precise gene-editing technologies, […] any change in DNA is scientifically feasibly detectable. […] any type of change in DNA, whether it's natural or made in the laboratory, is detectable scientifically.*

One may keep in mind that even "small" changes such as a single nucleotide insertion or deletion (indel) may have "large" and nonlocal consequences, and that such influence is not even considered.

2.2) Genome edition,
Edition does nothing more than modifying the shape of a text (size of the margins, fonts, type, and so on). It does not change the text nor the meaning, nor mainly write it from scratch. Did any editor of a scientific journal modify the text of a scientific article? No. Using such wording aims at promoting the idea that « genome edition » does something plain in a very well known context. Only the shape would be marginally changed.
Yet, meanwhile, the modified plants and animals are promoted as having drastic changes by scientists! We are even sold the end of hunger, drought resistance wheats, and the paralytics healed? Such a wording is misleading, and we will no more use it.

2.3) Is NBT a kind of "Breeding"?
The definition of breed is

> *to propagate (plants or animals) sexually and usually under controlled conditions*
> (Merriam Webster).

So breeding is multiplying plants or animals. The choice of the plant/animal kept by the breeder cannot be denied (*controlled conditions*). But it operates afterwards (*a posteriori*). On the contrary, "NBT" operate *before* the occurrence of the plant/animal (*a priori*). Like transgenesis, it makes or designs a plant/animal before it appears (*a priori*) according to a given will, an intention.
We keep two things:

> NBT is intrinsically different from breeding (*a priori* versus *a posteriori*);
> NBT is a genetic (and/or epigenetic depending on the molecular tools used) modification.

As a consequence, NBT produce Genetically Modified Organisms (GMO).
In a first step, one can wonder why do companies and researchers use the saying NBT for something that is not a breed? One may guess from the consequences. If NBT crops are « bred », they should not be regulated. It happens to be their interest that they defend, a *pro domo* rhetoric, but so, they want the citizens not to distinguish these altered plants genomes and thus they distort the meaning of the words. We can understand scientists who want to keep their plaything (and it is not only financial):

> « There is a great deal of potential research investment in the UK that could come from food technology industries, and any concerns about the safety of these foods could jeopardise this huge investment. So we can understand why scientists would be very anxious about jeopardising that investment. »
> Richard Horton, Editor of *The Lancet*, Channel 4 News, Friday 15 October 1999.

All those who mix the words collaborate to this task of misleading people. We claim it is a lie. More or less aware.
In a second step, we miss something: the intention of the scientists who design nature as if it was a product that they made up (*Misnaming an object is adding to the misfortune of this world* according to A. Camus). By hiding their will or intention, the real philosophical investigation on their role is made impossible. GM plants/ animals appear from nowhere and we are summoned either to accept them or to... refuse them but be forced to eat them without any label that would have preserved our informed choice. Such a political position is neither ethic, nor acceptable nor *politically* stable. In

French, we have a saying that "Intention matters". Although one maynot know intentions, neglecting them is a crucial error.

In addition to the two points above, we have seen:

> The proponents of « NBT » have an interest in twisting the words: unlabel those GMOs;
> Their interest is to hide their will to power, to « render alike masters and owners of Nature » (Descartes)

Below, we will no more use the NBT acronym but NTGEM for New Technique of Genetic or Epigenetic Modification.

2.4) Resistant or Tolerant crops

For the last twenty years, we have been reading proposals of crops « resistant to insects » or even « tolerant to insects ».

What are those crops? They have been designed/built up so as to produce a protein (Bt) that has an insecticide function. So the plant, when growing, produces a toxin that kills some insects. We do not bemoan the death of insects. We claim the crops are neither resistant nor tolerant to insects. They *kill* insects. Obviously, it is easier to sell to lay people a tolerant or resistant crop than a killer crop. But this use of the words is not inadvertent. It is on purpose that industrial but also researchers have modified the language to ease the acceptance or more precisely to prohibit from discussing.

Let us take an image. Imagine I am a GM (Bt) corn. Imagine an insect approaches me. I kill it and when the police comes, I tell the policemen I was either resistant or tolerant to this insect. Any serious policeman will consider I am lying and even kidding. Why scientists (advised by Public Relation companies) and industrials are considered as more serious than me as a GM corn?

3) What is behind the techniques?

3.1) Do NTGEM produce natural organisms?

One may read, for instance in a Danish report the rather contradictory statements[20]

> *The new plant breeding techniques are a continuation of an old practice […] New plant breeding techniques and precision breeding of our crops are relatively new concepts within plant breeding.*

Below, we reply to the claim that NTGEM act as Nature. We will not discuss whether NTGEM are « a continuation of an old practice » or not because anything can be claimed, but not one is definitive.

3.1.1) Taken from Nature?

The CRISPR system, modified for its use in genomes and epigenomes alterations, requires a Cas-like enzyme, a guide RNA (gRNA), a PAM DNA sequence to anchor near the sequences to modify, and often a template DNA. Some things must be noticed :

> Crispr-Cas systems originate from the bacterial' kingdom;
> not one CRISPR sequence was noticed in eukaryotic cells (plants, animals);
> Even though some immunity factors against invasive DNAs viruses are present in eukaryotic cells, such as the RNAi, there is no proof there be any common ancestor.

CRISPR takes place in procaryotic organisms and was extended to eukaryotic organisms with numerous changes among which merging the crRNA (crispr RNA, a 17-20 nucleotide sequence complementary to the target DNA) and a tracr RNA, which serves as a binding scaffold for the Cas nuclease. All this is *synthetically* merged into a sgRNA often denoted as gRNA (guide RNA). This merging does not occur in Nature. A company selling CRISPR molecules explains[21]:

20 https://pdfs.semanticscholar.org/2471/4de4b7bd877949e4bf1818545838941d853b.pdf

21 https://www.synthego.com/guide/how-to-use-crispr/sgrna

an sgRNA is a single RNA molecule that contains both the custom-designed short crRNA sequence fused to the scaffold tracrRNA sequence. sgRNA can be synthetically generated or made in vitro or in vivo from a DNA template.
While crRNAs and tracrRNAs exist as two separate RNA molecules in nature, sgRNAs have become the most popular format for CRISPR guide RNAs.

Moreover, it needs several related techniques as well as several vectors - with generally DNA scars into the genome - to introduce DNA, mRNA or proteins contaminated by DNA, to cultivate cells, to screen by using antibiotics or herbicide resistance traits to isolate the modified cells, to remove these resistance genes, to develop a plant callus and then regenerate plants… Can we deduce from this series of these related steps that it is *natural* in eukaryotic cells? We do not think so, though we do not contest it performs changes.

The repairing mechanisms of bacteria have been hijacked from their normal processes in the direction scientists wanted.
If one claims NTGEM come from nature, which is true, then one must acknowledge that, meanwhile, they were processed and – at *minimum minimorum* – much changed for application to eukaryotic cells. The process is no more the same and claiming it is natural is a lie.

3.1.2) The (denial of) intention
It was already justified in Section 2.3 that the description of the techniques denied the intention, so as to look « natural » and so prohibit labeling. Here we come back to the description of the techniques.
Indeed, when we order the cell to make "itself" a modification, we do not do it ourself.
But we did not do nothing neither.
So as to look « natural », some scientists say they do not modify the cells. But they acknowledge they put in the cell either the CasX RNA or the DNA's gene that will produce the CasX RNA. In the latter case, they make a preliminary transgenesis that inserts the genes associated to some of the involved proteins. It is then the proteins and the cells that make "by itself" the modification (that scientists designed!).
It looks like a child who pushes a table that makes fall a vase and says it is the fault of the table if the vase is broken, not his fault!
The goal is to hide on the one hand the intention and the will to power and on the other hand some persons: the *homo faber*, the scientist. We claim it is not a humility, but even a kind of pride. The techniques must be known even in details so as to make up one's opinion.

3.1.3) The sequencing techniques
Genetics and the several sequencing methods are facing numerous challenges. Either the sequencing method is rather accurate such as the Sanger method, but time consuming and very costly. Or it is less expensive per nucleotide, but the accuracy is lower such as for the NGS techniques. Technicians have to sequence in deep or ultradeep and are generally unable to detect large rearrangements. All this requires also programs that will not give the same results.
Afterwards numerous issues have to be faced to, such as assemble the DNA fragments, compare them… particularly with genomes with a high number of repetitive sequences and when numerous reference genomes have not been already sequenced and carefully annotated.

In addition, genetics and genomes are only a short part of the story. Epigenetics is not visible … because we cannot not see it easily. Sequencing methods for epigenetics are newer, less stable… and more costly. The same applies for epitranscriptomics.
What about the mere genetic and their sequencing techniques? The search for unattended mutations and rearrangements, unattended on-targets changes and of course the most famous off-targets (see 3.3) relies unfortunately either on

the cheapest but highly biased methods (with *a priori* knowledge) that use sofwares that try to match the subdivisions of the genome (each got by PCR) so as to build up back the whole genome. The longer the overlapping sequences the better the reconstruction. But it is never perfect. The programs do not behave the same way and so provide a reply more or less likely; unbiased methods based on full genome sequencing. The liability depends on the technique used (see above). Either cheap (but not very reliable) such as NGS or very expensive (but very reliable) such as Sanger's.

The abstract of an article states[22]:

> *Using long-read sequencing and long-range PCR genotyping, we show that DNA breaks introduced by single-guide RNA/Cas9 frequently resolved into deletions extending over many kilobases. Furthermore, lesions distal to the cut site and crossover events were identified.*

This proves that using better tools gives results that did not appear with inefficient tools.

The French ethics committee reminds that[23]:

> *a sequence of correct quality should be checked about 30 times, and if it is of very high quality (such as a clinical exome) 100 or 200 times.*

A review article recalls some of the limitations of sequencing, genome assembly and in particular that[24]:

> *Depth of coverage is affected by the accuracy of genome alignment algorithms and by the uniqueness or the 'mappability' of sequencing reads within a target genome*

In addition, one requires one or more reference genomes found in databases. Unfortunately, some of such references still contain numerous errors. For instance, the genome of plants with numerous repeated sequences can have been badly assembled and some of these non-coding sequences are involved in genes' expression. Sometimes, it is already GM plants that are sequenced and taken as a reference.
What about the results of all these hidden steps? To decrease the costs of sequencing, companies are generally using reference genomes instead of sequencing the variety's genome before they alter it. The comparison is then not relevant.

So the « technical » question of the sequencing technique, the programs or the databasis used to reply to a regulation question may hide irrelevant replies prone to trigger errors, troubles or even large problems. For all these safety reasons, labelling of organisms modified by NTGEM and publication of the entire protocol used are necessary precisely because detection is difficult. It is also advised by researchers from FDA (see 4.2).

3.1.4) Foreign DNA?

We are often proposed to consider NTGEM as a mere mutagenesis (in the classical meaning of irradiation or exposure to a mutagenic chemical agent). Since *in vivo* random mutagenesis was exempted (but never labeled as such!), it would be profitable to companies that NTGEM (though they are *in vitro*!) be considered alike any mutagenesis so as to hide them. Moreover, while transgenesis brings some foreign DNA material, this does not happen in (conventional) mutagenesis. But companies and researchers claim this foreign DNA does not remain. So, if there were no (remaining) foreign DNA, some argue that NTGEM would be similar to mutagenesis.

First, we must raise the question of why transgenic (and some others) GMO were labeled in the 2001/18EC Directive. Is it because of a foreign DNA or not ? Careful reading of the Directive shows

22 Kosicki, M., Tomberg, K. & Bradley, A. *Nature Biotechnol*. http://doi.org/10.1038/nbt.4192 (2018). https://www.nature.com/articles/nbt.4192

23 Advice n° 124 https://www.ccne-ethique.fr/sites/default/files/publications/ccne_avis_124.pdf

24 D. Sims *et al.* Sequencing depth and coverage: key considerations in genomic analyses, *Nature Reviews Genetics* volume 15, pages 121–132 (2014) https://www.nature.com/articles/nrg3642

that labeling of GMO is based on the technique used (and also novelty) and on what this technique enables. Whether foreign DNA is used or not does not matter. For instance if one takes one version of the growth hormone's gene in the salmon, and put it back, say 14 times, through transgenesis, the salmon will be denoted as transgenic and so GMO. No matter where the DNA comes from. The technique alone is relevant for discriminating. One of the reasons is that « the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination »[25].

Moreover, mainly the « recombinant nucleic acid techniques » were considered in the Directive[26]. We claim that « recombinant nucleic acid techniques » designate any technique that recombines nucleic acids, including those using even proteins such as CasX. The list of Annex IA Part 1 is « *inter alia* » (non-exhaustive) and so can be considered as including these NTGEM.

Is there any foreign DNA in NTGEM?

Due to the rather low transformation efficiency, most of the NTGEM still need to select the transformed cells. For that purpose DNA encoding herbicide or antibiotics resistance genes are integrated. Some companies or researchers attempt then to discard these genes by using integrases such as Cre-Lox. But generally they do not check whether everything, including the usual scar of insertion nor DNA removal, has been effectivey discarded.

The alteration tool such as Crispr-Cas9 is a very large molecule (protein), which is generally delivered by an *Agrobacterium* plasmid (still the most efficient tool), generally integrating the CasX gene as a foreign DNA into the genome. After expression, some companies attempt to remove these DNA sequences or knockout the Cas9 gene, but generally they do not look for any other scar of the integrated DNA fragments nor of course of the knockout or removal (see 2.1.5).

To decrease the risks linked to using DNA, some companies are attempting to use mRNA to deliver the Cas enzyme, a less efficient transformation system. In some instances, reverse transcription has been observed with DNA integration. Yet, the DNA contaminating the mRNA preparations, is almost never searched for into the genome[27].

Finally, the last and less efficient method uses Cas proteins to directly modify the plant genomes. Unfortunately, as is well documented for the Taq polymerase used in PCR, all proteins are contaminated by DNA, generally bacterial DNA. When companies claim no foreign DNA is used, they are clearly misleading. When they claim there is not remaining foreign DNA they are misleading too. In any case, this distinction has no legal relevance. The presence of this contaminating DNA is rarely looked for in genomes after their modifications.

The answer is thus effectively more complex than claimed by companies because most NTGEM use intermediate (intended or not) DNA. Some of this DNA remains, but is not necessarily looked for, and even removal lets some scars that are parts of the signature of the technique. Moreover NTGEM make a change that will make a secondary change, additionally to frequent foreign DNA integration. Industrials and scientists claim they did not do the secondary change (see 3.1.2). It is both right and false. Anyway, the only right thing is that if they did nothing, nothing would happen. So we do claim they did a genome alteration and even a (more or less intended) modification. The best proof is that they claim to have done it from before (*a priori*). And even, they claim they deserve a patent.

As was explained above, a (preliminary) transgenesis is often applied. It brings some intended or not foreign DNA. According to the EU regulation, it should be sufficient for the regulators to consider

25 Definition of GMOs in Art. 2 of Directive 2001/18EC made more precise in the Annex IA and IB.
26 Annex IA Part 1 (1) of Directive 2001/18EC
27 See also Sec. 3.3.1 for goat and bovine DNA inserted from the mere serum.

these organisms as regulated, although some European authorities cannot read and apply the directive (see the Belgian example below of a CRISPR corn).
Should there be no transgenesis, the DNA contaminated protein complex (CRISPR – Cas) is inserted in the cell and then this complex forces the cell to make (itself?) modifications designed by the scientist. Assume the proteins and RNA are taken off after. Assume too that it did nothing else than what it was designed to do. There remains something that was not naturally present before : the Genetic Modification.

3.1.5) The order of the sequence.
The genome is not only a sequence of nucleotides. It is organized through nuclear sub domains. For instance, the order of some genes makes a difference[28]. The 3D organization of the genome is currently under scrutiny with the Topologically Associated Domain (TAD) which makes that two sequences of two chromosomes must be spatially close for one of the gene to express a protein.
It is often claimed that the location of genes « precludes interactions between genes on different chromosomes. » Yet, a recent article

> « report[s] a marked divergence from this pattern of nuclear organization that occurs in mouse olfactory sensory neurons [and] shows that olfactory receptor gene clusters from 18 chromosomes make specific and robust interchromosomal contacts that increase with differentiation of the cells. These contacts are orchestrated by intergenic olfactory receptor enhancers»[29]

As for “junk” DNA[30], a still recent wording, or intron with regulating sequences of their genes, numerous parts of the genomic language are currently under scrutiny. If one does not look for safety at the right place, can one claim it is safe ?
The recent concept of pangenome per species proves that all of that has a global meaning.

3.1.6) About proteins?
The central dogma of molecular biology was that information went from DNA to RNA to protein and never in any other direction. Now, we do know it is wrong. Since protein can modify the behavior of a cell (and even of organisms), it is irrelevant to distinguish DNA, RNA and proteins as a modifying agent. So no matter what type of molecules (that could even be synthetic, such as PNA[31] or nanomaterials already used for genome modifications[32]!) is used to modify the organism or cell. The definition of 2001/18 in its Annex IA part 1 lists non-exhaustively some of the techniques implying a (regulated) GMO:

> « recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation; »

We claim proteins such as CasX are included in the « recombinant nucleic acid techniques » since they recombine nucleic acids. So, such techniques produce (regulated) GMOs owing to the Annex IA part 1. The « genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination » (Directive 2001/18EC) and parts of the unintended changes remain unknown.

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28 *Nature Genetics*, vol 22, p 90 as reported in *News Scientist* May 8th 1999 https://www.newscientist.com/article/mg16221851-900-even-with-the-right-gene-you-might-not-see-green/
29 K. Monahan *et al.* *Nature* **volume 565**, pp. 448–453 (2019) https://www.nature.com/articles/s41586-018-0845-0%C2%A0
30 Of course « junk DNA » is not junk. Considering that if we do not know what it does, it means that it does nothing is a deep epistemological error.
31 Peptide Nucleic Acid
32 https://www.biorxiv.org/content/10.1101/805036v1 and https://www.newscientist.com/article/2222028-exclusive-spray-on-gene-editing-could-make-genetic-modification-easy/

3.2) NTGEM related/associated techniques

3.2.1) Regeneration techniques

Assume we have modified a cell and let the cell try to regenerate a whole plant. It does not work for most of the species and even for some varieties into the same species. The reason is that the cells of those “recalcitrant” plants or varieties do not naturally differentiate to a pluripotent stem cell before a callus, step necessary toward a whole organism. Nobody knows how it really works, but it is a common experiment that organisms (including humans) are not only a set of cells and that the environment must be much controlled, even for a plant’s cell, to differentiate! It is why numerous cooking recipes are developed in labs and why an international symposium was launched in London in 2016 about these limiting steps. There are, at that stage of the process, numerous techniques that we call related techniques hidden in the protocol (such as Cas9 delivery, cell selection and encoding genes removal after selection, see above). They are summarized by micropropagation.

What problems do raise these techniques?

Assume, for instance, after a mutagenesis has been applied to cells, that they are later multiplied. It is well known that there are *less* (unwanted) mutated genes with some mutagenesis than with cells and tissues multiplication (the so-called somaclonal variation)! By neglecting these regeneration steps, one does not see the whole protocol.

We can understand that private researchers do not want to mention it. But what can we think of public researchers who do not speak more of it?

3.2.2) Preparation techniques

In a preliminary step, the genes are inserted in a plasmid (circular DNA usual in bacteria) which is inserted in a bacterium. Then it is multiplied in this bacterium on unreferenced medias serums. A first possibility (quite usual indeed) is the insertion of the whole plasmid or even the insertion of chromosomal sequences from the bacterium. In the animal domain, some goat or bovine genes have been recently shown to be transmitted from the serum during the (claimed to be precise and accurate!) NTGEM because of this undescribed step[33] in the protocol.

We include these preparation techniques inside the related/associated techniques too.

These techniques are considered as negligible by scientists who give more value to the novelty of research than to the mere techniques. They favor Science to Technique. They will let their technicians apply the related techniques because it is not their main center of interest. It is not despite they are researchers, but precisely because they are researchers and that cooking recipes are mastered by technicians and engineers. Large parts of this know-how of a lab are less favored in scientific articles. We do not know whether they contempt these techniques, and those who apply them, but they have no interest in popularizing these facts. Moreover, not mentioning these steps prevents from questioning large parts of the technique.

One must remember that the NTGEM have various non-negligible related techniques in the whole protocol that must draw attention.

3.2.3) Repairing mechanisms

One more « technical » point is often neglected. It is the repairing mechanism. The NTGEM break the DNA in a double strand break (DSB) in the host DNA. Various mechanisms exist then so as to repair these DSB: HDR, NHEJ, alterNHEJ/MMEJ...

It happens that HDR is less error prone than the NHEJ. So a vague description of « repair mechanism » is no way to know what was effectively performed, including trustworthiness, both from a safety point of view and from a political point of view (know what is done).

33 Ono *et al.* 2019 https://www.nature.com/articles/s42003-019-0300-2.pdf *Communications biology* (2019) 2, art. 57 https://doi.org/10.1038/s42003-019-0300-2 This article will be analyzed below more deeply.

Currently, reading a patent does not allow to understand which method was effectively used. All this hides several biases to the regulators and risk assessors.

We want the whole protocol (full material and methods) of preparation, mutation and regeneration to be made public for any inscription at the seed catalogue.

3.3) Side effects
We will focus only on nuclear changes since unfortunately the unintended changes of plasts' genomes, such as mitochondria or chloroplasts, are not examined, a regrettable lack for risk assessment.

3.3.1) Off target and on target unintended modifications
Do the NTGEM perform only what they are said to perform? One must indeed reply in a negative way.

Any modification technique has a target sequence. But other locations may have a very similar sequence and the NTGEM may make a mistake. Such errors, of rather small size (Indels for Insertion or Deletions), are called off target and induce pleiotropic effects. A basic reason is that there is no perfect GPS for proteins in such a forest and they must knock at numerous doors before finding the right one. So, sometimes, a wrong door is opened[34]. This is a huge domain partly documented on the genetic (not so much on the induced epigenetics changes). Particularly when we take into consideration, beside these indels, other off-targets mutations such as chromosomal rearrangements which are generally not detected, particularly when using NGS sequencing methods or using non-efficient software to detect potential off-target sites.

Since the genes of interest (whether the one of Cas or of another protein involved in a NTGEM protocol), generally accompanied by those of selection are multiplied in bacteria, it may also happen that a chromosomal bacterial gene (or sequence) be inserted. In an article among 93 mice modified by NTGEM and analysed, 57 carried mutant alleles (61 % errors is a lot!)[35].
The inserted (host!) DNA consisted of mouse repeats, including mouse short interspersed nuclear elements (SINEs), mouse long interspersed nuclear element-1s (L1s), mouse *endogenous retroviruses* (!!), and mouse satellite repeats and simple repeats. There were captures of DNA sequences deriving from retrotransposons, genomic DNA, mRNA and sgRNA.

More recently the same research group showed that DNA from the *E. coli* genome can integrate in the target organisms' genome[36] as it was already shown for *Agrobacterium* chromosomal sequences, beside the delivery plasmid. Acquisition of *E. coli* DNA was found to be quite frequent. Insertion of long unintended DNA sequences occurred at 4% of the total number of edited sites and 21% of these were of DNA from the *E. coli* genome. The source of the *E. coli* DNA was traced back to the *E. coli* cells that were used to produce the vector plasmid. In addition, this paper proves that edited mouse genomes *can acquire bovine DNA or goat DNA*. This was traced to the use, in standard culture medium for mouse cells, of foetal calf serum; that is, body fluids usually extracted from cows. This serum contains DNA from the animal species it happened to have been extracted from, hence the insertion in some experiments of goat DNA (which occurred when goat serum was used instead of calf serum).

34 Of course, the forest and door is only an image. But the sentence « The guide RNA [...] recognizes the target DNA region of interest and directs the Cas nuclease there for editing. » on the website of a company selling CRISPR tools, is misleading. To remain in the image, no GPS has ever directed you anywhere. It is still you who steer the vehicle and you might make errors even if the GPS's advice is perfectly right.

35 https://www.nature.com/articles/srep12281 Ryuichi Ono *et al. Scientific Reports* **volume 5**, Article number: 12281 (2015)

36 Ono *et al.* 2019 https://www.nature.com/articles/s42003-019-0300-2.pdf C*ommunications in Biology* (2019) 2, art. 57 https://doi.org/10.1038/s42003-019-0300-2

Due to the less advanced state of research for plants, it is highly probable that such observations could be made for plants, provided such searches be performed.

More worrisome, amongst the DNA sequences inserted into the mouse genome were bovine and goat retrotransposons (jumping genes inducing mutations particularly when cells are stressed) and mouse retrovirus DNA (HIV is a retrovirus). All the same, CRISPR-treated human cells are associated with mutations in the tumour-suppressing protein p53[37] or loss of p53 function[38]. Thus gene-editing is a potential mechanism for horizontal gene transfer of unwanted pathogens, including, but not limited to, (retro)viruses.

The unwanted DNA may come from inside the edited cell, or it may come from the culture medium, or it may come from any biological material added to the culture medium, whether accidentally or on purpose.

Is the whole process so precise and accurate as claimed by the companies and even researchers?

3.3.2) On target unintended modifications

When the NTGEM operates, it breaks the DNA at a more or less specific sequence. Errors elsewhere than in the target location are designated as off target. But even when there is no error outside the location, there may be added DNA at the right location. It may come either from the cell (see the repeats depicted above), or from the plasmide (see above) or even from the serums where the bacteria was cultivated (see above).

Several errors have been observed in on-target sequences: from chromosomal rearrangements to foreign DNA unintended insertion. Despite being less documented as less searched for and more difficult to detect, the unintended genomic alterations remain.

The abstract of an article states[39]

> *Thus far, exploration of Cas9-induced genetic alterations has been limited to the immediate vicinity of the target site and distal off-target sequences, leading to the conclusion that CRISPR–Cas9 was reasonably specific. Here we report significant on-target mutagenesis, such as large deletions and more complex genomic rearrangements at the targeted sites in mouse embryonic stem cells, mouse hematopoietic progenitors and a human differentiated cell line. Using long-read sequencing and long-range PCR genotyping, we show that DNA breaks introduced by single-guide RNA/Cas9 frequently resolved into deletions extending over many kilobases. Furthermore, lesions distal to the cut site and crossover events were identified. The observed genomic damage in mitotically active cells caused by CRISPR–Cas9 editing may have pathogenic consequences.*

When transgenic plants were proposed, they were supposed to be not only alike Nature, but also much safer, more precise. Since ZFN techniques emerged, transgenics is considered as very unprecise. Since CRIPSR emerged, ZFN are considered as very unprecise. The emergence of Prime CRISPR enables its author to write « *the wildly popular CRISPR–Cas9 gene-editing tool alters genomes, it's still somewhat clunky and prone to errors and unintended effects.* »[40]. Their prime CRISPR offers *« much lower off-target editing than Cas9 nuclease at known Cas9 off-target*

37 Ihry RJ et al. (2018). p53 inhibits CRISPR-Cas9 engineering in human pluripotent stem cells. *Nat Med* 24, 939-946, doi: 10.1038/s41591-018-0050-6 https://www.nature.com/articles/s41591-018-0050-6

38 Haapaniemi E et al. (2018). CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response. *Nat Med* 24, 927-930, doi: 10.1038/s41591-018-0049- https://www.nature.com/articles/s41591-018-0049-z

39 Kosicki, M., Tomberg, K. & Bradley, A. *Nature Biotechnol*. http://doi.org/10.1038/nbt.4192 (2018). https://www.nature.com/articles/nbt.4192

40 Hedi Ledford, Precision CRISPR tools could tackle host of genetic diseases, *Nature*, Vol 574, 24 October 2019 pp. 464-465

sites »[41]. Are we forced to believe the last speaker or does the ethical question not depend on the technical details ?

3.4) Epistemological point of view on Science

More philosophically speaking, if scientists cannot see something, it is out of their scientific scope. So, it is not an issue and so they behave as if it does not exist, at least inside their discipline. Let us stress that the implicit assumption is that only what scientists can measure (with their limited tools) are topics of scientific interest. What if the laboratory extends to the whole world as in a genetic experiment of massive dissemination?

This point of view prevents oneself from seeing some things (because of the limited tools or their restricted use). So scientists may deny these things exist because they do not see them, because it is out of their scope, because they restrict their scope. Seeing them would require to have a look and take the right tools. But those tools are numerous, complex to master and expensive (see above Section 3.1.3). Meanwhile, scientists claim "reality" is only what is measurable and what they accept to measure.

Refusing to consider what cannot be measured with a (partial) list of techniques is an intrinsic bias to science since it is so coupled to Technology that it is sometimes difficult to split them. In the case of NTGEM some scientists claim they did not find any off target effect, but they usually choose a very limited tool/program (see the case of the hornless bulls of *Recombinetics* in Section 4.2 as a good example of what can be missed when the industrial's opinion prevails).

So, our objection is twofold. On the one hand, the choice of measurements is too restricted. On the other hand, even if the best tools were used, not only other tools (to be developped) should restrain from being too categorical, but even one may not exclude that some properties cannot be measured (for instance if they are qualitative).

4) Case studies

Below we report the examples of a plant, an animal and an insect. They cast a harsh light on what happens in reality and not only the propaganda[42].

The case of animals is widely documented in a recent report from GeneWatch[43].

4.1) A CRISPR corn

Roughly speaking a corn was genetically modified by CRISPR/Cas9 in a biotech laboratory in Belgium (VIB) so as to delete some basis from a gene known to naturally repair the DNA! Let us quote the version made public after the ECJ trial of July 25th 2018[44]:

> « A CRISPR/Cas9 gene cassette, necessary to induce the desired mutation, was introduced into maize plant by means of *Agrobacterium tumefaciens* mediated transformation. Transformants containing the gene cassette and the desired mutations were selected, and by means of conventional crossing with wild-type plants the CRISPR/Cas9 gene cassette was removed by selecting T1 plants that only contained the desired mutation, but no longer contained the gene cassette (null-segregants). The plants in the field trial therefore do not contain foreign genetic material. They only contain the desired frameshift mutation. »

The research laboratory described more precisely the process[45]:

41 Anzalone, A. *et al.* Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature* *h*ttps://doi.org/10.1038/s41586-019-1711-4 (2019).

42 One may notice that *Propaganda* was the title of Edward Bernays' book. He founded the Public Relation companies and states in his book : « Propaganda, by repeatedly interpreting new scientific ideas and inventions to the public, has made the public more receptive. Propaganda is accustoming the public to change and progress. » (last sentences of Chapter X).

43 http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/GeneWatch_UK_response_to_the_Nuffield_Council_on_Bioethics_fin.pdf

44 see https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/crispr_mais_bijlage_11_snif_0.pdf and the WIV-ISP/41/SBB_2016_0445 report

45 source http://www.bio-council.be/Advices/BAC_2019_0242.pdf

> « The three maize lines were obtained using a vector containing the CRISPR-Cas9 genes on a T-DNA construct. The T-DNA construct used for transformation also contains a bar gene that served as a marker for the selection of transformants after *Agrobacterium tumefaciens*-mediated transformation. The bar gene [confers glufonisate resistance]. The vector backbone contains a spectinomycin resistance marker gene. »

In less twisted words, the CRISPR-Cas9 genes and two transgenes were put in the plasmid of an *Agrobacterium tumefaciens* bacterium that genetically modifies plants. This preliminary transgenesis inserted an antibiotics resistance gene, an herbicide resistance gene, the gene of Cas9 and the one of the guide-RNA[46].
So a (preliminary) transgenesis is done, that triggers a protein that does the (secondary) modification. The (preliminary) transgenesis is forgotten and not called as such. The (secondary) CRISPR modification is described as a[47]

> « mutagenesis induced by the transient presence of the CRISPR/Cas9 system [...] that is a technic of genetic modification that *does not involve the use of recombinant nucleic acid molecules* or *genetically modified organisms »* (we stress).

Indeed the (secondary) modification does not involve the use of recombinant nucleic acid molecules. But the very first does and it is not mentioned. Moreover, the detection strategy used for assessing the removal of herbicide resistance gene provides only a partial response about a fully functional whole gene, but nothing about more or less truncated, not functional sequences, located elsewhere. In other words, the detection strategy for resistance genes may prove the gene is inserted and effective because the cell survives. But it is not symmetric when one wants to prove the gene is no more present (such cell would die). Even in her paper mail of August 1st of 2016 to the Belgian Minister of Environment, Kelly Lardinois states that (bold is not ours):

> « **Intermediate plants,** in confined use, containing an exogene cassette of T-DNA that encodes for the components of CRISPR/Cas9 must be considered as **GMO**. »

So the SBB knows. Why does it not say it the same way to the public and in its conclusion?
The SBB report claims that:

> « When the T-DNA cassette encoding the components of the CRISPR/Cas9 system has been effectively segregated away, the SBB is of the opinion that the resulting plants should not be considered as GMOs in the meaning of the GMO regulatory framework » (p. 1/7 of Annex2)

So the very first "mutation" is, indeed a (preliminary) transgenesis. The SBB claims that if the transgene is segregated away, it is no more a GMO. No legal statement supports this claim. Should transgenesis do only what it is supposed to do (no off target and so on), putting the "cassette" and then taking it off would be like doing nothing?
One might wonder why they did anything then !
Moreover, if we enter a room, put everything upside down and then get off, are we allowed to say it is as if we had not entered?
It is a pity that we must come back to so simple examples to show the dishonesty of all those who speak and write about new GMOs (and so many other things too).

The same report /annex (p. 4/7 Regulatory considerations) states rightly:

> « The exclusion of these techniques/methods is possible only on the condition that they do not involve the use of recombinant nucleic acid molecules or GMOs. Plants genetically modified by conventional mutagenesis techniques are therefore exempted from the EU GMO legislation. The main argument underlying this exemption is that these techniques have conventionally been used in a number of applications and have a long safety record (recital 17 of Directive 2001/18 EC) ».

46 One may wonder why doing a transgenesis if you have the so marvellous tools of NTGEM. The transgenesis is used to insert the (small) DNA of (larger) proteins. The proteins could not be forced to enter the vegetal cell (nor the protoplast where the cell wall was stripped), but the DNA can. So CRISPR-Cas will still require transgenesis for a while.

47 p. 1/7 of annexe 2 of the Advice of the Biosafety and Biotechnology Unit (SBB), the official Authority that applies the regulation in Belgium (WIV-ISP/41/SBB_2016_0445) July 5th 2016.

It means that the intention (not using recombinant nucleic acids) prevail on the facts: some DNA has been inserted and some parts may have been unintentionally let (as observed for instance for the hornless cattle) but the SBB excludes of regulation. Isn't it an *ideological* claim presented as sound science that such a CRISPERized corn is not regulated?
How can anybody knowing the question not see that

> the CRIPSR-Cas9 corn involved the « use of recombinant nucleic acid molecules » (even if they are segregated away later);
> the intermediate plants were GMO (as said above even by SBB);
> there is no accurate and convincing demonstration that crossing discarded all the foreign inserted DNA[48];
> the quotation of Directive 2001/18 is right that exemption applies only if the plants « do not involve the use of recombinant nucleic acid molecules or genetically modified organisms » (Annex IB). But since there is an « intermediate » GMO, all its progeny will be regulated as GMO from the Directive. This seems not to be known by the authority;
> CRISPR is claimed to be a technique that « have conventionally been used in a number of applications and have a long safety record (recital 17 of Directive 2001/18) » while it was invented in 2012 and that more and more scientific papers show unintended modifications beside the scars of the associated techniques.

The first transgenesis was hidden because presented as a « transform » or « a transient presence » (not accurately demonstrated). It was very likely not seen by the politics because of the Authority. But the words were « twisted by knaves to make a trap for » politicians and citizens (*If* Kipling).

Despite all what is said above, we may quote the Advice of July 5th 2016, on this corn:

> « The SBB is of the opinion that the genetic modification achieved in the plants to be released in the field as described in the present request are *similar in type and extent to those that can be obtained via natural or induced* (using chemical or physical agents) *mutagenesis*. Genome editing in plants using the CRISPR/cas9 system as described in the present request can thus be considered as a form of mutagenesis » (we stress).

We fear it is even the trust in "authorities" that is being undermined by such statements. Such an *ethical* problem is never raised. Indeed it is political too. If there comes a day when the population no more trusts the authorities, the political stability could be very much weakened.

4.2) Animal's case
Cattle farming is often made in very small space. So the bovines may hurt the others of the herd. These cows can be injured because they are crammed into despicable conditions. Scientists from *Acceligen*, a subsidiary of *Recombinetics* (Minnesota) have considered putting a gene that induces that the bull (and the cows bred by it) is hornless.

Instead of letting more space to the animals (our favored solution, that is simple and non-technical), one considers genetically modifying cattle.

So, the company claimed that it had used "genome editing" (TALEN in this case and as usually with a preliminary transgenesis) to insert this gene, then clone two such bulls (so there is cloning too!)...

48 One must understand that the resistance gene occurence/absence detection is not symmetric. If one wants to detect the occurrence of a resistance gene, one pours antibiotic on the cell. Either it survives and will be used in the process, or it dies. But if one wants to prove either that it has not this sequence or that it is not functional elsewhere, one may not pour antibiotic (dead cells are useless). Only the whole genome sequencing and appropriate programs can find right off targets or on targets. No scientific claim can be done out of this.

The company stated in 2017 to Bloomberg that « We have all the scientific data that proves that there are no off-target effects »[49] as already claimed in *Nature* in 2016[50].

Moreover, *Recombinetics* argued that the American regulation of transgenic animals by the FDA « makes no sense: hornless cattle made with gene editing, *it argues*, are identical to what you could get by crossbreeding dairy cows with naturally hornless cattle »[51]. In 2016, it asked the FDA to consider its hornless animals as GRAS - i.e. made from ingredients "Generally Recognized As Safe", such as salt, calcium or DNA itself!

The company did not make any specific declaration about this GM animal because it contested any regulation. It means that a company is self-assessing its risks without any external expertise thus without legal frame. By chance the FDA recently proposed guidelines for NTGEM animals that are very similar to european regulation for any organisms[52].

Meanwhile, Alison Van Eenennaam, a veterinarian at the University of California and *Acceligen* collaborator, provided evidence to the FDA as to whether the "surplus" animals could go to the slaughterhouse. Since incineration costs about $1,300/animal, she preferred to earn money by selling it as steaks rather than paying to incinerate it. So she sent the sequencing of a bull.

Were the genetic modifications made "at [their] exact location"?

FDA scientists checked the bull's genome and published their results[53]. It appears that

> The (whole) plasmid genome of a bacterium used for this « genome edition » had also been inserted;
> An insertion of the modification model (« repair template sequence ») is present twice on a chromosome;
> In this genome, a resistance gene to several antibiotics (ampicillin and neomycin/kanamycin) remained from the bacterial plasmid.

FDA scientists report that « Integration errors are under reported » … As FDA scientists say:
« Recent examples of previously unexpected alterations are complex genomic rearrangements at or near the target site in mammalian genome editing experiments[54] [55]. The complex rearrangements include insertions, deletions, inversions and translocations that were difficult to detect by standard PCR or DNA sequencing methods. ».
The last sentences insist on what we previously reported in Section 3.1.3 on the sequencing programs and processes that are not all relevant.

4.3) Mosquitoes' case

Malaria is a disease caused by a parasite profiting by the bite by a mosquito of a human to multiply. It causes severe symptoms including fever, tiredness, vomiting and headaches. In severe cases it can cause yellow skin, seizures, coma or death.

49 https://www.bloomberg.com/news/articles/2017-10-12/this-genetics-company-is-editing-horns-off-milk-cows
50 https://www.nature.com/articles/nbt.3560
51 *MIT Technology review* March 12th 2018
52 https://www.infogm.org/6872-united-states-precautionary-principle-gm-animals (commented in a note below)
53 Alexis L. Norris *et al.*, Template plasmid integration in germline genome-edited cattle, Biorxiv https://doi.org/10.1101/715482
54 Shin, H.Y. *et al.* CRISPR/Cas9 targeting events cause complex deletions and insertions at 17 sites in the mouse genome. *Nature Commun* 8, 15464 (2017)
55 Kosicki M., Tomberg, K. & Bradley A. Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. *Nat. Biotechnol* 36, 765–771 (2018)

Nobody may doubt the wish to diminish the deaths by cause of malaria, but victimism does not prevent from arguing and critically assessing the risk-benefits balance.
Some years ago, we were already sold the « solution » of transgenic mosquitoes (by Oxitec). Such mosquitoes were *made* to be sterile and released in Jacobina Brazil. As says Jeffrey Powell, professor of ecology at Yale University, « The claim was that genes from the release strain would not get into the general population because offspring would die »[56]. Laboratory tests had shown the females that mated with the genetically modified males only produced offspring about 3% of the time, and the survivors were feeble and were believed to be unable to reproduce. J. Powell adds that « Based largely on laboratory studies [and not only on limited mathematical models], one can predict what the likely outcome of the release of transgenic mosquitoes will be, but genetic studies of the sort we did should be done during and after such releases to determine if something different from the predicted occurred. ».
Tens of millions of such mosquitoes were released in Jacobina. Did it work as foreseen? The Yale study[57] showed not only that offspring from the transgenic mosquitoes had reproduced but also that the population of mosquitoes in Jacobina is now a mix of their original types plus those from Cuba and Mexico, likely leading to a more robust population, according to the researchers. Moreover, the population of mosquitoes, after initial decline, had rebounded about 18 months after introduction of genetically modified males.
One must notice that the related/associated technique (see Section 3.2) of crossing the line of mosquitoes with other lines (Cuba and Mexico) was not mentioned and should have prohibited to evaluate scientifically the whole protocol.

5) Detection problems / traceability
The Industry claims that[58]:

> *The conclusion is that these gene editing formats should not be regulated more strictly than traditional breeding or conventional mutagenesis techniques that have been used safely in agriculture and industry for thousands of years and decades, respectively.*

We must remember that there are two types of traceability. The standard one (ISO 22005, ISO 9001) is based on documents and their transmission. The other on detection and identification laboratories methods of what is authorized or prohibited. This is a set of tools to verify products' compliance and to fight frauds. This set of methods provides the background of what was called for the already approved GMOs the "analytical traceability".
It is always possible to enforce a documentary traceability. Some people are right to object that if there is no way to identify new GMOs, it would be illusory to force to label them[59]. We were said the same in the 2000's for transgenic GMOs. Fortunately, some scientists and industrials have made research to provide identification methods that are routine work nowadays. In 2018, the European commission (EC) was requested to launch such a program of research for new GMOs, but refused to fund it despite the trial of July 25th 2018 that clarifies that new GMOs are *regulated* GMO. It would be easy to request an official claim from the company that its plant is GMO or not and the whole protocol used to make it if it wants to be registered in the official catalogue of seeds and put fines in case of lies that could be proved later. By its refusal of funding appropriate research, the EC could be declared legally binding of refusing to provide informed choice to the European consumers.
The lack of political will, not to say the refusal of any coercion to the biotech industrial sector, can also be seen in the fact that, in 2003, even the UK government thought of forcing those who would

56 https://news.yale.edu/2019/09/10/transgenic-mosquitoes-pass-genes-native-species (news hidden by Yale, but the content can be found elsewhere)
57 Evans BR *et al.* Transgenic *Aedes aegypti* Mosquitoes Transfer Genes into a Natural Population. *Sci Rep*, 9(1), (2019). 13047. doi: 10.1038/s41598-019-49660-6. https://www.nature.com/articles/s41598-019-49660-6
58 http://www.efbiotechnology.org/images/uploads/gene_editing_pp.pdf
59 For instance « With respect to traceability, it will not be possible to separate mutations resulting from SDN-1 from mutations occurring by traditional means, unless information about their gene sequences is available. » from Dec. 4th 2018 report from Aarhus University report for the Danish government. https://pdfs.semanticscholar.org/2471/4de4b7bd877949e4bf1818545838941d853b.pdf

sell GMOs to insert also a genetic bar code with the transgene[60]. There is no reason for not forcing companies that want to sell new GMOs to put such bar codes or an equivalent if it is the will of citizens, if it is proven such codes can ensure analytical traceability and are as safe.
So it is not because there is not yet any general method of identification that one must give up. Some articles have given tracks of what type of research to do. In an article[61] on this topic, Y. Bertheau, founding partner and former member of the European Network of GMO Laboratories (ENGL) and of its Steering committee, summarizes that each technique has side effects which altogether can be used to detect and identify a product and the NTGEM method at its origin. Each technique of modification (whether insertion or deletion) lets various scars. None of them can, isolated, be sufficient to identify the technique used. But if one gathers all the informations of these scars, it is possible. While in routine only one molecular trait can be used to screen and detect a NTGEM product, the process of accurate identification – called "matrix approach" - proceeds essentially by gathering several molecular information, essentially the same way as for identifying people through fingerprinting (ca 150 information characteristics are used for a fingerprinting based identification) or facial recognition[62]. These gathered molecular traits can be more easily handled using a DSS[63]. He concludes[64] that the

> *proof of concept of the ability to identify NBT techniques at the origin of certain products should be readily available as soon as the European Commission decides to provide the means as in the late 1990s with research programs on transgenesis issued GMOs. As 30 years ago for transgenic GMOs, the analytical traceability and labeling of NBT products is technically accessible; it is part of a political choice and therefore partakes in the balance of power between stakeholders.*

Larry Gilbertson, Bayer's scientist confirms that[65]:

> *it is scientifically feasible [to detect organisms obtained by NBTs] because in all of these methods, whether it's classical breeding, random mutagenesis, or these new precise gene-editing technologies, we're making precise changes in the DNA and we know the changes that we're making [are] scientifically feasibly detectable.*

This is confirmed in an article dealing with human biology where we care more of the off target effects[66]:

> *Each mutational process, defined by DNA damage and DNA repair components, leaves a characteristic pattern or mutational signature on the tumour genome. The final mutational portrait of each patient's cancer is determined by the intensity and and duration of exposure to each mutational process. As an analytical principle, mutational signatures have gained considerable traction, and are regularly featured in cancer genomics literature. Already, there are multiple algorithms to extract mutational signatures, though each has its own mathematical idiosyncrasies [and] mutational signature research has progressed remarkably.*

So even if there is not yet a protocol to identify the technique with which a GMO was produced, there will come a day when it will be possible. Does the EC fund such research ? Not yet.

In addition, one may remember that if we export some living organisms (such as seeds), we must

60 https://www.newscientist.com/article/dn3377-britain-may-force-dna-barcodes-for-gm-food/
61 New Breeding Techniques: Detection and Identification of the Techniques and Derived Products. In book *Encyclopedia in food chemistry. Reference Module in Food Science* Elsevier January 2019.
62 In simpler words, one's height does not characterize a person, nor one's eye color, nor … But all these parameters may characterize the person.
63 Decision Support System
64 Same reference as above
65 https://www.euractiv.com/section/agriculture-food/video/bayer-scientist-regulation-and-risk-assessment-must-evolve-with-technology/
66 X. Zou *et al.* Validating the concept of mutational signatures with isogenic cell models. *Nature Communications* (2018) 9:1744 DOI: 10.1038/s41467-018-04052-8

apply the Carthagena Protocol on biosafety to the convention on biological diversity. In this Protocol, modern biotechnology is defined as

> *the application of:*
>
> *a.* In vitro *nucleic acid techniques, including recombinant desoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or*
>
> *b. Fusion of cells beyond the taxonomic family,*
>
> *that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection;*

So as to be able to trade with other commercial partners, we must label and keep the information of the whole protocol that made the organism.
It is interesting to read Belinda Martineau who was the chief scientist at Calgene where she developed the very first GMO, the tomato FLAVR-SAVR[67]:

> *There are many imprecise aspects of genetic engineering, many related to our very incomplete knowledge about genetics and genomics. That is why regulation of every product of this technology should be required and why they should be labeled. [...] developers of GM foods can already voluntarily label their products just as we did at Calgene. […] when science moves out of the lab and onto the plates of consumers we must be more cautious about it. We scientists must explain what is imprecise and could pose potential problems as well as what is precise about the technology so that society as a whole can make informed decisions about how to use and regulate such a technology.*
>
> *There is not enough transparency about genetic engineering technology right now and that contributes to consumer wariness about it.*

6) Claims and lies
Since the 2000', the claims are the same:

1. save Humanity from hunger;
2. have plants growing in deserts;
3. enable small breeding companies do the GMOs to protect our SME against the large American companies in a new kind of anticapitalism supported by biotechs[68]!
4. it is not possible to differentiate, so why should we label?
5. if the other countries (like US) make use of them, our Small and Medium Enterprises (SME) will be weakened in the global market.
6. GM crops increase the profitability for farmers.
7. Patents guarantee return on investment.

We briefly reply to these claims that may have been supported by honest people.
Concerning point 1, why would companies make up a GMO for non-creditworthy people? Why giving things to the South if we don't want them? Would it be a trick to blame the refusal of these GMOs and then make the North accept them? Were the patents given to the South so as to let small peasants keep their seeds and make them more autonomous?
There has been a believable project of a GM sweet potato. But some natural lines already resistant have been used thanks to the fact that seed banks had kept seeds for sharing many lines of potatoes. They came on the market much before the GM line worked. This project was only for propaganda of a company.
A scientific article also replies to this claim[69].

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67 https://non-gmoreport.com/articles/march2014/scientist-journey-from-gmo-believer-to-skeptic.php

68 For new GMOs, for instance, « only major companies can afford the costs and, hence, only these companies can probably make commercial use of the new SDN technologies » from Dec. 4th 2018 report from Aarhus University report for the Danish government. The report proposes not to regulate new GMOs so as to ease the development of SME. No hint is given to prevent the « major companies » from profiting even more of this deregulation. https://pdfs.semanticscholar.org/2471/4de4b7bd877949e4bf1818545838941d853b.pdf

69 Y. Bertheau Feeding the World: Are Biotechnologies the Solution? (2015) Chapter 6 https://onlinelibrary.wiley.com/doi/10.1002/9781118864463.ch06

We do not deny the possibility that new GMOs might *help*[70] to solve hunger even though industrials are of bad faith. But the question is not to decide whether we will promote new GMOs or let people starve (as most media report). The question is to arbitrate between promotion of peasants' autonomy, crops adapted to local fooding, or of biotech crops and patents. In an infinite world where time, energy and money is infinite, one should go in all the directions. But we are in a limited world (this is not a sad news indeed). Instead of wondering only what we could lose if we do not stride to GM crops, we must compare with what we can gain by striding to alternative crops! Comparing a loss and no loss is unfair. Moreover the right questions is to know what, each of these possibilities (and others) will provide to each one (peasants who need autonomy, consumers, …), to what term and with risks for whom? Evaluating a balance requires at least two possibilities to compare.

Concerning point 2, no GM crop has grown in deserts. The drought tolerance is more complex than claimed by companies and conventional breeding by the CIMMYT drives to more tolerant crops than the one of biotech companies.

Concerning point 3, when the large companies hide themselves behind small ones, it is not fair. Particularly when SMEs are tied up by the patents of the worldwide companies. Testbiotech writes on June 24th of 2019[71]:

> « The US corporation (with its agribiotech sector renamed Corteva) has allegedly signed contracts with all the important owners of basic patents on CRISPR/Cas technology. Data presented in a meeting with the EU Commission at end of 2018 show that DowDuPont has successfully managed to combine 48 patents on the most basic tools in one patent pool. According to DowDupont, access to such a high number of patents is necessary in order to apply the technology in plant breeding to its full extent.
> […]
> DowDuPont is now in the unprecedented position in plant breeding of being able to allow other companies access to the patent pool and demand licence contracts: what on the one hand is promoted as the 'democratisation' of patent law, is on closer scrutiny emerging as nothing less than a way of controlling competitors and securing a dominant market position.
> DowDuPont is fast becoming the gatekeeper of an international patent cartel. ».

Moreover, large companies own the key patents and SME are forced to ask for licences, justifying their research, its utility and profitability. The commercial licences are negotiated according to the productivity of the plant and the possible refusal gives a strong position to the owner of the patent as is classical. So, by splitting research, evaluation and commercial activity, the final step enables the the owner of the patent to set the rate of the licence according to what the SME can hope. Patents are definitively a way for the largest to control/buy the smallest even if the latter can negotiate the price of their company. They do not take the risks and they control the SME that take it.

Concerning point 4, we may remember that, despite the initial claims, there are scientific processes to identify the (transgenic) GMOs. Moreover, « the British government [was] considering forcing biotech companies to use DNA bar coding to identify genetically modified organisms »[72]. If we don't look for methods, we will not find any.

Concerning point 5, we must acknowledge that this did not happen. European Union so far developed a very strong position in the non-GM seeds market and its agriculture is moving toward a more agroecological strategy that is attempting to avoid pesticides and of course the associated

70 The claim of solving hunger is definitely stupid.
71 https://www.testbiotech.org/en/news/patent-cartel-large-companies
72 *New Scientist* Ferburary 13th 2003 https://www.newscientist.com/article/dn3377-britain-may-force-dna-barcodes-for-gm-food/

NTGEM products. Moreover, are we forced to act as our American neighbor only because it is strong? The trust in politics could decrease of invoking such arguments.

Concerning point 6, when a major problem such as the spreading of Palmer Amaranth in the USA triggers huge costs[73], we wonder whether these costs were taken into consideration by industrials and regulators. Who will bear the costs? In the same spirit, how can anybody know the price of the nuclear kWh if we do not know the price of retreating radioactive waste?

Concerning point 7, one must acknowledge two truths. First, the guarantee of Return On Investments (ROI) increases technical innovation, and unfortunately it is now the main driver for funding even basic research. The second that the more a company has power on the market by having monopoles (should they be limited in space and time as in patents), the more this will reduce innovation. As was justified by J. Bessen and R. Hunt, the main question is the interdependence of innovations in the field[74]. The more innovations are interdependent in the field, the more patents will impede innovation. In addition, the mere existence of patents and the fact that patent offices cannot know all the already known « techniques » and products, the most « innovator » in patents will profit by the whole system. This may even let patents on already existing « native traits ». There are such examples[75]. Consequently, patents increase capitalistic concentration and a loss of economic diversity. Diversity is a trait of a more resilient economy.

7) Eugenism

Despite the precision of the Darwin statements, his cousin Galton was in favor of a new science that was taught throughout Europe : eugenics or « practical Darwinism »[76] or « social Darwinism »[77]. Almost all geneticists in Europe and the United States until the Second World War were eugenicists. In the United States, eugenics was taught in 375 American universities and colleges in 1928[78]. Sterilization of people with disabilities was also encouraged in the United States[79], was legal in Germany during the Second World War and was still legal until 1972 in Sweden, a socialist country where the government knows what is good for the people.

If there had been ethicists at that time, they would have invited scientists who would all have been in favor of this sterilization. Would it be right yet? Ethics does not reduce to a vote. It is not like democracy. When it comes to changing the world to come, or even genetically modifying the humans, the opinions of unborn children are essential. Can we make a decision on the future of humankind without their advice?

Let us remind that if one transforms a property (like giving birth) into a process, the next step will be to control it, then to optimize it.

Optimizing birth is eugenics.

One could object that there will still be the possibility to have birth naturally. It would be an « added freedom » (as if freedom could be counted and measured up to the number of chocolate brand in the supermarkets). But if some children are the *product* of the *will* of their/his (!) parent, he or she will

73 It may be summarized here that after some years of Roundup Ready crops in the USA alternating between soy and corn, the ecosystems were faced to Roundup every year. As was announced by any ecologist, some mutant plants such as « Glyphosate-resistant (GR) Palmer amaranth infested […] 75 % of scouted cotton area […] in Arkansas, Mississippi, and Tennesse. » Riar *et al. Weed Technology* (2013) 27:778–787.

74 James Bessen and Robert M. Hunt (2007), An Empirical Look at Software Patents, *Journal of Economics and Management Strategy* 16, no. 1, pp. 157-89 http://papers.ssrn.com/sol3/papers.cfm?abstract_id=461701. More can be read in French http://www.ogmdangers.org/action/brevet/arg_brevets_complet.html.

75 For instance Gauthier Semences had a breeder's right on a lettuce isolated for its resistance to aphid. The company Rijk Zwann obtained later a patent on such a trait and prohibited the company from selling its lettuce for this trait.

76 The saying is from Thomas Huxley. See a recent article in N. Comfort *Nature* **574**, 167-170 (2019) https://www.nature.com/articles/d41586-019-03014-4

77 Francis Galton

78 https://www.nature.com/articles/530418a

79 « Three generations of imbeciles is enough » written in the *Buck* v. *Bell* Supreme court case so as to legitimate the eugenic laws thoughout the USA.

be reduced to be a product. It suffices that some of his or her trait will have been chosen. Even if his or her life will be « better » (to be defined), he or she will know he or she is no more free[80].
Is it only by chance that Robert Edward, test-tube baby pioneer and Nobel Prize for this claims[81] :

> *Soon it will be a sin of parents to have a child that carries the heavy burden of genetic disease. We are entering a world where we have to consider the quality of our children.*

Among many others, one may add Lee Silver, Professor of molecular biology at Princeton, describing the future in which the GenRich (genome enriched) are opposed to the Naturals[82] :

> *The GenRich - who account for 10 percent of the American population - all carry synthetic genes [...] that were created in the laboratory […] All aspects of the economy, the media, the entertainment industry, and the knowledge industry are controlled by members of the GenRich class [...] Naturals work as low-paid service providers or as laborers, and their children go to public schools [...] If the accumulation of genetic knowledge and advances in genetic enhancement technology continue [...] the GenRich class and the Natural class will become […] entirely separate species with no ability to cross-breed, and with as much romantic interest in each other as a current human would have for a chimpanzee.*

On the opposite, Hannah Arendt speaks of[83]

> *This future man, whom the scientists tell us they will produce in no more than a hundred years, seems to be possessed by a rebellion against human existence as it has been given, a free gift from nowhere (secularly speaking), which he wishes to exchange, as it were, for something he has made himself. There is no reason to doubt our abilities to accomplish such an exchange [...]. The question is only whether we wish to use our new scientific and technical knowledge in this direction, and this question cannot be decided by scientific means; it is a political question of the first order and therefore can hardly be left to the decision of professional scientists or professional politicians.*

H. Arendt denounces that the increase in the control of the generational process will lead to eugenics that will reduce children (and all humans) to the product of a will, giving power to the will over the body. Is it not the *will to power* that has motivated the dark ages in Europe?
Distinguishing States' eugenism and markets' eugenism is only relevant to stress that if one opposes markets' eugenism, then one may be said to be antidemocratic. This already happened to us. Disturbing a conference on genetic modification of humans, we were said to be antidemocratic by the TV show. We take responsibility for this. This process is typical of a narcissistic and hyper-individualist society[84].

8) Conclusion

It was proved (see Section 2 *Some words*) that the wording « cut and paste », « genome edition », « New Plant Breeding », « tolerant crops » were twisted and even distorted. It happens to mislead in the interest of scientists and industrials!
Even more, behind the (main) technique are hidden various related/associated techniques either in the preparation and delivery of the DNA/RNA/gRNA/templates, in the modified cell selection or in the regeneration of the whole plant (see Section 3 *What is behind the techniques*). The techniques do not produce natural plants (3.1), were hijacked from what happens in the bacterial's kingdom (3.1.1), the intention/will is hidden (3.1.2), the sequencing tools and methods are more or less precise (3.1.3), some foreign DNA is used but denied (3.1.4), the order of the sequences matters (3.1.5), both

80 See *GATTACA* or *Blade Runner* where those who are born are free while those who are made are not free. The question is not technical to know whether the process makes errors. In GATTACA, a hero is faster at race than the others. But he knows he has been designed for an intention. So he is no more free because he always compares to the ideal of what he believes the others expect from him. Freedom is not an individual property. It is a political property.
81 *The guardian* Sept. 1999 https://www.theguardian.com/society/1999/sep/22/guardiansocietysupplement2
82 *Re-Making Eden* New York: Avon Books (1998). pp. 4-7
83 H. Arendt *Human condition*, The University of Chicago Press (1958)
84 See among others C. Lasch *The Culture of Narcissism: American Life in an Age of Diminishing Expectations*, or watch the documentary on Edward Bernays *The century of the self* (on the internet) or read his book *Propaganda*.

preparation and regeneration methods constitute related techniques and specific risks (3.2), knowing the repairing mechanisms matters for accuracy (3.2.1-3.2.3), various side effects (both off target and on target) occur, and, last but not least, the way science is practiced (epistemological point of view (3.4)) proves that intrinsic biases are not seen (3.3). All of theses facts have unexpected consequences denied by industrials while they appear in real life (see section 4 *Three examples* on plants, animals and insects). Yet the scientists, whether close to industrials or not, claim that at least some NTGEM (SDN1 for instance) would be not distinguishable from what happens in Nature. We replied to those statements in Section 5 (*Detection problems and traceability*). Roughly speaking, one may not claim that what he does is the same as Nature and claim it is a breakthrough that enables patents and added value! One may object that the proof that a plant was modified by CRISPR or TALEN is impracticable yet and so that analytical traceability for fighting frauds is illusory. We replied that a documentary traceability can always be done. Indeed it will not be scientifically based and likely to be escaped by industries if there is no checking identification techniques. But there are already hints that if, as it was the case for transgenic plants, the Commission funds researches so as to develop identification techniques that are already drafted, there will be results as there have been for transgenic plants. According to our informations an American company should launch a technique to identify Cibus canola within months.
Various claims and lies were reminded in Section 6. Eugenism as a consequence of the technicization of the generation was discussed in Section 7. It is unescapable if the procreation is transformed into a process even only for non-human animals. It paves the way for the worst.

Last we want to escape from the trap of arguing only « scientifically ». On the one hand, the word « Science » is a very distorted word, as for “junk science” and “sound science” also used by “doubt merchants” companies[85]. By confusing science and technical innovation, companies and some public researchers are misleading lay people and confiscate a certain political debate. Of course, this must not prevent from hearing the scientific arguments. But they are sometimes voluntarily misleading. On the other hand, science may not reply to any question. Politics and ethics is above. Of course labeling is important for measuring and controling the risks. It is also important for our international obligations (Carthagene Protocol) towards other countries. But, besides the discussion on risks, we do support on the one hand mandatory labelling of NTGEM plants similarly to the 2001/18 EC Directive since even the FDA plans to enforce it for animals in the USA[86] and on the other hand prohibition of any NTGEM modification of humans and even of animals.

Concerning the plants, we, as consumers and citizens, want to know what we eat and to have an informed choice as recognized by the Aarhus convention. And as friends of peasants, we support their right to know what they sow. Concerning the humans we make no difference between State’s eugenism and market’s eugenism. In any case, the child (and so any human) is reduced to be the *product* of a will as says H. Arendt.

We do base our position not only on the risks but also on our will to know the world where we live. It is not only a safetiness concern, but even a freedom concern.

Very sincerely yours

85 N. Oreskes, E.M. Conway, *Merchants of doubt* (2010) Bloomsbury Press

86 In its latest draft guidelines of regulation, the american FDA proposes to regulates GM animals (whether transgenic or NTGEM) in a way very similar to the 2001/18EC directive on (vegetal or animal) organisms. If the americans are as strict, the Europeans could keep their regulation as it is (or reinforce it by including the modifications through proteins). https://www.infogm.org/6872-united-states-precautionary-principle-gm-animals