Submission to the New Zealand Parliament Health Committee on the Gene Technology Bill 2024

This submission is from Claire Robinson of GMWatch, a not-for-profit civil society organisation based in the UK, and Michael Antoniou, Professor of Molecular Genetics and Toxicology at King's College London, UK.[1]
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We object to the New Zealand government's intention to exempt from the requirements of the GMO (genetically modified organism) regulations those genetically modified organisms that it terms "minimal-risk products of gene editing, for example, products of editing techniques that result in organisms that cannot be distinguished from those produced by conventional processes".[2]

While the government claims that its proposed regulation would be "risk-proportionate" on the basis that these GM organisms "cannot be distinguished from those produced by conventional processes", this claim is based on assumptions that these GM organisms

- cannot be distinguished from conventionally bred ones, and
- pose no risks beyond those posed by their conventionally bred counterparts.

In order to change these assumptions about the relevant GMOs into legally sound and scientifically based facts, the applicant must be required to *prove* that their GMO cannot be distinguished from conventionally bred organisms and therefore poses minimal risk. The applicant must therefore be required to provide

- Long-read and deep whole genome sequencing, which is generally seen in the scientific community as the best way of capturing unintended large-scale deletions and rearrangements, as well as unintended insertions of foreign DNA that can be missed by the more frequently performed short-read sequencing.[3]
- "Omics" molecular compositional analyses (proteomics protein profiling, metabolomics biochemical profiling) should be required to be performed, to ensure that the GMO is truly compositionally, including nutritionally, equivalent to the non-GM parental organism with the exception of the intended genetic modification, that no unexpected toxins or allergens have been created in claimed-exempted plants, and that no unexpected allergens have been created in claimed-exempted animals. There is broad scientific support for this approach.[4]

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[1] Note: This report reflects Prof Antoniou's own personal opinions and does not express the views or opinions of King's College London.
[2] https://www.legislation.govt.nz/bill/government/2024/0110/7.0/whole.html#LMS1009756
[3] For example, see: https://plantmethods.biomedcentral.com/articles/10.1186/s13007-020-00661-x ; https://pmc.ncbi.nlm.nih.gov/articles/PMC9655061/ ; https://www.sciencedirect.com/science/article/abs/pii/S246845112300034X
[4] For example, see https://enveurope.springeropen.com/articles/10.1186/s12302-023-00734-3 ; https://www.frontiersin.org/journals/bioengineering-and-biotechnology/articles/10.3389/fbioe.2023.1276226/full ; https://www.frontiersin.org/articles/10.3389/fpls.2018.01874/full

Gene editing is more mutagenic than nature or random mutagenesis breeding

It is incorrect to assume, as the proposed legislation does, that some gene technologies (including those that the New Zealand government wishes to exempt from GMO regulations) produce conventional-like organisms. They may (though this is unproven) in theory produce conventional-like organisms, but many outcomes of the gene technologies in question will not be conventional-like.

Reviews of the literature and other scientific articles confirm that gene editing, including SDN1 and SDN2 applications, can produce organisms that are very different from the non-GMO parent, with different risk profiles. As well as the intended changes brought about by application of the gene technology, many unintended changes could result. Genetic changes could result in altered biochemistry, including the production of novel toxins or allergens, which could jeopardise human or animal health or the environment. Unintended genetic changes brought about by the processes of gene technology applications (including gene editing) must be identified and their consequences analysed. The logical and evidence-based conclusion of these reviews is that all organisms produced with these technologies must be subjected to a detailed risk assessment for health and the environment.[5]

Gene editing can produce changes that nature/random mutagenesis cannot

Reviews of the scientific literature confirm that gene editing can make changes in the genome that would not occur, or that would be highly unlikely to occur, in natural reproduction or in random (chemical- or radiation-induced) mutagenesis breeding. This is because some areas of the genome are protected from mutations, but gene editing can overcome these protections. Therefore these gene technologies can present new risks that must be assessed on a case-by-case basis.[6]

Research in plants has discovered that genetic variation arising from natural reproduction is not random but an adaptive mechanism that helps the plant thrive in its environment.[7] In contrast, gene editing is specifically designed to override natural protections against non-adaptive genetic variation and gives rise to mutations, in ways that do not happen in conventional breeding or are very unlikely to happen.

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[5] For example, https://enveurope.springeropen.com/articles/10.1186/s12302-023-00734-3 ; https://doi.org/10.3389/fbioe.2023.1276226 ; https://pubmed.ncbi.nlm.nih.gov/36365450/ ; https://www.mdpi.com/2223-7747/10/11/2259/htm ; https://doi.org/10.3390/biotech10030010 ; https://enveurope.springeropen.com/articles/10.1186/s12302-020-00361-2 ; https://doi.org/10.3389/fbioe.2019.00031 ; https://www.frontiersin.org/articles/10.3389/fpls.2019.00525/full ; https://www.nature.com/articles/s41587-019-0394-6 . Note that while many of these reviews focus on the EU situation, the evidence presented and conclusions drawn apply equally to New Zealand and other jurisdictions proposing to deregulate certain gene technologies.

[6] https://doi.org/10.3389/fbioe.2023.1276226 ; https://www.frontiersin.org/articles/10.3389/fpls.2019.00525/full

[7] https://www.nature.com/articles/s41586-021-04269-6

Gene editing is more mutagenic (genetically damaging) than traditional processes/nature and random mutagenesis breeding

It is often claimed that gene editing is less mutagenic (genetically damaging) than conventional reproduction processes and random mutagenesis breeding. However, this notion (which was always, in our view, contradicted by a large body of scientific evidence) is debunked by a recent submission to the New Zealand government as part of the public consultation on its gene technology deregulation proposal.[8] The authors of the submission, Prof Jack Heinemann and colleagues, show, via references to the peer-reviewed literature, that gene editing (including applications classed as "precision breeding") is far more mutagenic (in terms of mutation frequency) than nature or random mutagenesis breeding – see Table 1.

Claims that gene-editing procedures result in fewer mutations than traditional breeding are false, or at least, they are not generalisable to all gene-edited plants or all gene editing applications. This is illustrated by a rare study that compared the number of mutations in rice plants caused by the gene editing procedure (tissue culture; Agrobacterium infection-mediated cell transformation; action of the CRISPR/Cas gene-editing tools) to the number of genetic variants resulting from rounds of natural reproduction.[9] The scientists found that:

- Seed saved from traditionally bred non-GM rice plants following three rounds of natural reproduction had only 30 to 50 spontaneous gene variants per plant;
- Few off-target mutations were caused by the CRISPR editing tools – only 2 out of 49 plants had them;
- The gene editing-associated tissue culture process caused large numbers of mutations (200 per rice plant). Tissue culture is an obligatory part of making gene-edited (or older-style transgenic) plants;
- "Agrobacterium infection is mutagenic with a preference for introducing indels" (insertions/deletions of DNA). The Agrobacterium infection increased the number of mutations over and above the number caused by tissue culture. Agrobacterium infection is commonly used to make gene-edited plants.

While the scientists concluded that the gene editing tools were "highly specific" in generating targeted mutations, their experiments showed that the associated process of tissue culture and the commonly used process of plant cell transformation, Agrobacterium infection, caused far more mutations than the number of gene variations caused by natural reproduction. Therefore, insofar as risk depends on the number of mutations, it can be deduced that the risks of the gene editing process, taken as a whole, are greater than those of natural reproduction. Also, the authors' claim of "highly specific genome editing" is invalidated by their own results, since they ignore the large numbers of unintended gene-editing process-induced genome-wide mutations.

[8] https://ir.canterbury.ac.nz/server/api/core/bitstreams/0e1aa118-5e68-4b43-b395-2a4487d90aa4/content

[9] Tang X et al (2018). https://genomebiology.biomedcentral.com/articles/10.1186/s13059-018-1458-5

Some types of large-scale mutations resulting from gene editing may also occur in nature. However, such mutations occur at low frequency[10] and many harmful or neutral mutations will be selected out during long evolutionary history.[11] Other types of mutations resulting from gene editing would either never occur, or would be extremely difficult to produce, using conventional breeding or mutagenesis breeding techniques.

To quote one example: in Camelina sativa, which is an allohexaploid plant (having six sets of chromosomes from three different species), a complete knockout of all alleles of FAD2 (a gene that encodes an enzyme that produces polyunsaturated fatty acids in plants) was achieved using CRISPR/Cas9 gene editing.[12]

Kawall et al (2020) comment: "These changes would be extremely difficult, if not impossible to achieve using traditional mutagenesis or via spontaneously occurring mutations in nature. The camelina genome contains three subgenomes in two copies, thus each gene exists in six copies… To knock out all alleles of FAD2 by traditional mutagenesis, three complementary mutations in the FAD2 gene would have to be induced in each genetic locus in separate plants and subsequently each mutation made homozygous. Those mutant plants would then have to be crossed with each other in order to obtain a single individual plant that contains all mutations. Simultaneous generation of a homozygous triple mutation of FAD2 causing an effective gene knockout using chemical or physical mutagenesis is extremely unlikely, as is the occurrence of such a camelina plant due to spontaneously emerging mutations."

Kawall and colleagues emphasise that gene editing expands the range of possibilities beyond what conventional breeding and random mutagenesis breeding can accomplish – and with those expanded possibilities come greater risks, which must be carefully assessed on a case-by-case basis.[13]

Therefore, attempts to equate gene-editing-induced mutations to those occurring in conventional processes and random mutagenesis breeding[14] are not scientifically justified.

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[10] See, for example, Jian S-Y, Ramachandran S (2010). https://pmc.ncbi.nlm.nih.gov/articles/PMC2862397/ This paper states: "Generally, the ratio of natural mutation is very low at only 10^{-5}–10^{-8} in higher plants. However, a large collection is still available during long evolutionary history. Some of such mutants were harmful or neutral and might be lost during evolution." See also Jain SM (2010). https://tinyurl.com/ydert6dq This paper states: "The purpose of mutation induction is to enhance mutation rate in a short duration in developing new plant varieties. The occurrence of spontaneous mutation frequency rate is very low and difficult to use in plant breeding."

[11] Jian S-Y, Ramachandran S (2010). https://pmc.ncbi.nlm.nih.gov/articles/PMC2862397/

[12] Morineau C (2017). https://doi.org/10.1111/pbi.12671

[13] Kawall K et al (2020). https://enveurope.springeropen.com/articles/10.1186/s12302-020-00361-2 ; Koller F and Cieslak M (2023). https://doi.org/10.3389/fbioe.2023.1276226 ; Chu P and Agapito-Tenfen SZ (2022). https://pubmed.ncbi.nlm.nih.gov/36365450/ ; Kawall K (2021). https://www.mdpi.com/2223-7747/10/11/2259/htm ; Eckerstorfer MF et al (2021). https://doi.org/10.3390/biotech10030010

[14] https://dbtindia.gov.in/sites/default/files/Final_%2011052022_Annexure-I%2C%20Genome_Edited_Plants_2022_Hyperlink.pdf p.4.

The upscaling of mutations through gene editing and other GM technologies means increased risk over and above anything that nature – or even random mutagenesis breeding – can produce, as Prof Heinemann and co-authors explained in a peer-reviewed publication,[15] as well as in the recent submission to the New Zealand government.[16]

Trade implications

The UK imports a significant amount of food from New Zealand[17] and, while the UK government has deregulated certain subclasses of GMOs in England only,[18] New Zealand meat, dairy, and fresh produce retains a "clean green", healthy, and GMO-free reputation in the UK that should be preserved and not traded in for hypothetical and unproven future benefits.

Summary and conclusions

Even if it were possible, as is claimed, to produce the same genetic alteration through gene technologies as might occur through conventional processes and/or random mutagenesis breeding, there is clear scientific evidence to show that the spectrum of unintended genome-wide mutations will be different, both in quantity and in quality. In this regard, the process of gene editing, which is touted as being the least mutagenic gene technology, when taken as a whole, produces a greater number of unintended genome-wide mutations than arise through conventional processes of reproduction.

With regard to plants, given the different spectrum of unintended genetic mutations that can occur between various breeding techniques, each will carry its own range of risks. However, risks arising from unintended mutations from plant breeding techniques are not just a numbers game. What is crucial is the quality and consequences of the mutations. In contrast with conventional processes, gene technologies can intentionally or unintentionally modify any region of the genome and thus in principle carry a greater risk of altering gene functions with negatives downstream outcomes, in terms of production of novel toxins and allergens.

These scientific realities highlight that the process of gene technologies must be taken into account in assessing risk – not just the intended product. By way of analogy, electricity produced by fossil fuel stations as opposed to solar panels is the same product, but because the processes of generation are different, they pose different health and environmental risks and thus are covered by a different set of regulations.

In conclusion, the New Zealand government's proposal to deregulate gene technology processes and products is contrary to the science that underpins these

[15] https://online.ucpress.edu/elementa/article/9/1/00086/116462/Differentiated-impacts-of-human-interventions-on
[16] https://ir.canterbury.ac.nz/server/api/core/bitstreams/0e1aa118-5e68-4b43-b395-2a4487d90aa4/content
[17] https://assets.publishing.service.gov.uk/media/679903411c041dcc469dadf8/new-zealand-trade-and-investment-factsheet-2025-01-31.pdf
[18] https://bills.parliament.uk/bills/3167

methods. The science evidently says that there will be unintended large-scale DNA damage from the processes of gene technology, which need to be taken into account via robust regulations. There is no scientific justification for exempting certain classes of gene technologies from GMO regulation – to do so puts health and the environment at serious risk of negative outcomes. The existing GMO regulation can easily be adapted to take account of any differences in the properties or risk profiles of newer gene technologies, as compared with those that have been in use previously.