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

Summary analysis

- The scientific case is not made for the proposed reforms to gene technology law. The risk tiering framework is not risk proportionate. It would lower the regulatory burden but substantially increase risks to human health and the environment.
- We do not believe that replacing a process-based framework is justified because there has been no substantive analysis of the actual unique costs of current regulations or evidence provided that they impede innovation.
- Alternative process-based options that streamline compliance for work done in certified containment facilities would be more effective and affordable.
- The proposed reforms are based on idealised and superficial descriptions of gene technology. The idealised outcome of *indistinguishable from conventional breeding* is only one of many products made every time gene technology is used. The ideal outcome must be identified and confirmed from amongst the mix of organisms made.
- All other powerful mutagens, including chemical and radiation mutagens, are treated with significantly more oversight and control for safety reasons.
- Processes capable of creating similar *hazards* do not necessarily create similar *risks*. *Creating hazards indistinguishable from those which may be created by conventional breeding is not the same as creating risks indistinguishable from conventional breeding*.
- New Zealand would have the most extreme combination in the world of proposed species breath (microorganisms, plants, animals) and process (e.g. SDN2) exemptions without the safety net of a case-by-case confirmation step prior to release.
- What constitutes equivalent risk outcomes to conventional breeding should not be left to secondary legislation. Risk can only be effectively mitigated by continuing to require that gene technology be used only in certified containment facilities and that outcomes are confirmed to meet release criteria.
- The Bill includes provisions to erode the prerogative of New Zealanders to have a determinative say in what risks of gene technology are acceptable.

Recommendations

- Remove *exempt activities* as a risk tier.
- Make **all** repeat/serial or multiplex reaction processes notifiable activities.
- Require that **all** activities, including exempt and non-notifiable, are conducted inside certified containment facilities.
- Require that **all** outcomes of gene technology are assessed for risk on a case-by-case basis or are confirmed to meet exemption criteria prior to release.
- Introduce a specific obligation of the proposed Regulator to require that evidence provided to prove that an organism meets the exemption criteria or satisfies the risk assessment is of the highest scientific standards and is current with the most recent scientific techniques.

Terms

AM1	United States regulatory category "AM1: An indel or contiguous deletion of any size, made at a targeted location, with or without insertion of DNA if generated without using a repair template, or without insertion of DNA if generated using a repair template."
AM2	United States regulatory category "AM2: A plant with up to twelve (12) modifications, made simultaneously or sequentially, if each modification individually qualifies for exemption and occurs in a different gene."
Containment	Certified containment facility operated with trained and accountable personnel. It can be a laboratory but has more specifications than a laboratory as defined by the Hazardous Substances and New Organisms Act. A laboratory that is not at least physical containment level 1 can be a residential kitchen, primary school science classroom, garage, fenced paddock, or campervan with respect to environmental release and human exposures.[1]
Epigenetics	Epigenetic inheritance is defined as cellular information, other than the DNA sequence itself, that is heritable during cell division. [1]
EU	European Union
FDA	United States Food and Drug Administration
FSANZ	Food Standards Australia New Zealand
Gene/genome editing	The use of gene technology to direct the location of change in a genome. Terms ODM, SDN and SDN1-3 refer to gene editing.
GMO	Genetically modified organism
Mutation breeding	Use of chemical or radiation mutagenesis
NAS/NASEM	United States National Academies of Science/United States National Academies of Science, Engineering, and Medicine
NBT, NGT	New Breeding (e.g. Australia) and New Genomic (e.g. Europe) Techniques. Generally, synonyms that include the use of gene/genome editing, gene silencing, and other techniques.
ODM	Oligonucleotide-directed mutagenesis. A gene editing technique based on (usually) a synthetic oligonucleotide that does not use a site-directed nuclease.
Oligonucleotides	Short polymers of nucleic acids, DNA or RNA or a mixture.
Reagents	The necessary, inseparable, or facilitating chemical ingredients in gene technology procedures.

[1] The HSNO Act (2020) definition of laboratory is only that it is "*a vehicle, room, building, or any other structure set aside and equipped for scientific experiments or research, for teaching science, or for the development of chemical or medicinal products.*"

RIS	Regulatory Impact Statement Reform of Gene Technology Regulation Ministry of Business, Innovation and Employment 31/07/2024
SDN	Site-directed nuclease
SDN1	Repair of site-directed nuclease activity without a nucleic acid template.
SDN2/SDN3	Repair of site-directed nuclease activity involving nucleic acid templates to guide repair of SDN action. The two differ by description of the template used.

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Introduction

This submission is from the Centre for Integrated Research in Biosafety at the University of Canterbury. The research centre has approximately 20 years of experience in the subjects of gene technology governance, risk assessment and risk management, capacity building, and practical work in genetic engineering.

Authors of this document are both practitioners in the technical art and participants in risk assessment, regulation, and policy at the international and national levels. One author has among other things served the High Court as an expert witness in its 2014 decision *Sustainability Council Trust v. EPA*, was the expert witness for the Auckland Unitary Plan and Whangarei and Far North District Plans, UC representative to the Royal Commission on Genetic Modification. At the international level, on this topic the same author served the Convention of Biological Diversity's Ad Hoc Technical Expert Group on Risk Assessment and Risk Management for over 10 years, provided commissioned reports to the United Nations Commission on Genetic Resources for Food and Agriculture (FAO), and served on the Expert Working Group of the Swiss National Academies of Science on the topic of genetic engineering, amongst other contributions.

We do not confine ourselves to technical aspects of gene technology. As our name suggests, we integrate research from different disciplinary perspectives to arrive at an understanding of the complexities, and sometimes over-simplifications, of problems presented to government for policy solutions. Our transdisciplinary insights and contributions have been tested in the international peer-reviewed literature.

We wish to speak to this submission at the Select Committee.

We reserve the right to provide supplementary submissions that expand on the content of this submission.

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[2] Prepared in accordance with the Critic and Conscience of Society and Academic Freedom Policy (2024). This may not be the opinion of the University of Canterbury. The authors are grateful for comments from Dr Elvira Dommisse and Simon Terry. We thank Prof David Williams (Karl Kirchgessner Foundation Chair in Vision Science, UCLA David Geffen School of Medicine) for peer review. The authors made final decisions about content.

Overview

The proposed Bill is poorly designed to achieve its stated purpose. We encourage the Select Committee to consider more practical and effective strategies. In our view, modest reform of the status quo offers the greatest opportunity and lowest cost.

There is an option to build upon process-based regulation without it being the status quo,[3] the only process-based option provided in the Regulatory Impact Statement (RIS). For example, the enabling row of the options table on page 50 of the RIS could have been written as "*This option would maintain all products in scope of regulation being subject to" confirmation that products meet exemption criteria or benefit from a risk assessment risk management plan prior to release*[4] instead of as "*This option would maintain all products in scope of regulation being subject to stringent premarket assessment and approval, limiting the ability to deliver beneficial outcomes for New Zealanders.*" By using the example of the status quo for all process-based approaches, the RIS invites the reader to agree with the choice of a "hybrid" option.

The proposed legislative trigger for a regulated tier is products and processes that create outcomes *distinguishable from conventional breeding*. This trigger inevitably leads to future semantic disputes of what conventional breeding means, and technical challenges to distinguishability. These debates and contests aren't focussed on safety and are not efficient ways to regulate.

We suggest that solutions be sought not in the hybrid approach but in reform of *risk categories*.[5] The right mix of triggers keeps within public control both products and processes that are or could be hazards. The right triggers would not allow high risk products to escape oversight, satisfying the criticism made in the RIS of outcome-based approaches. Process triggers would not necessarily lead to prohibitively stringent premarket assessment and approval, the criticism made in the RIS of process-based approaches.

The right triggers would ensure that regulatory measures would proportionally ramp up as a function of risk, rather than as a function of hazard [2].

The Regulator could still place some outcomes into pre-determined risk categories. The outcome may fall into these categories either because of documented conformity to criteria that ensures outcomes are of acceptable risk, or because the activity and the outcome are in certified containment facilities (e.g. the approach taken by India).

An advantage of this approach would be that it recognises that the tools themselves are hazards because they increase mutation rates in organisms. The tools are used safely only under conditions that prevent unintended exposures to them.

Another advantage of this approach is the relatively easy and cost-minimal transition from the status quo. Further advantages might include better opportunities for constructive tangata whenua and public engagement in setting the standards in secondary legislation while reducing regulatory requirements that produce marginal benefit for work in containment.

Regulation, not deregulation, advances use of safe biotechnologies. The Director of the United States Food and Drug Administration Center for Veterinary Medicine put it this way:

> At this early stage, as genome-editing technology is continuing to develop and the science is evolving, bringing products with unknown risks to market without adequate oversight to ensure

[3] According to the RIS (footnote 4), reforms of the Hazardous Substances and New Organisms Act were not considered because of Ministerial direction.

[4] Where "proportionality" is achieved through secondary legislation rather than exemption from primary legislation.

[5] This is also suggested by the US National Academies of Science, Engineering, and Medicine. See Chapter 1.

they are safe and that they produce the promised effects will undermine consumer confidence and, ultimately, set back the progress of the entire field. [3]

But all our friends are doing it

When the Minister introduced the Bill she said that "other countries have embraced gene technology, and it has potential to treat cancers, increase agricultural production, lower emissions, adapt to a changing climate, and, ultimately, grow the economy. Gene tech is already being used safely in 29 other countries, including many of our trading partners such as Australia, China, Japan, the US, Canada, and many European countries."

Gene technology is more than releasing genetically modified organisms (GMOs). In various ways it is being used safely everywhere in the world including New Zealand. However, this does not mean that it is exclusively used safely or that the track record of safe use would be as good without regulations.

According to the latest data from Food Standards Australia New Zealand (Appendix 1), when it comes to making GMOs only 31 (including New Zealand) of 195 countries (16%) have consultation processes underway that might - or might not - lead to changes in the equivalent of their gene technology laws. Only 11% (21 countries including Australia) have taken steps to change their laws. As of December 2024, the United States has reversed its legal position, reducing to 20 the number of countries revising regulations.

Of the 20 countries that have changed their regulations, 15 have taken the decision to reduce regulation on all species – microorganisms, plants, fungi, and animals. Many retain a case-by-case evaluation even if operationally they expedite some pre-defined outcomes. Only 2 of them, Japan and Australia, are in New Zealand's top 5 export markets at 5% and 16% by revenue, respectively. The remainder have amended regulations for use on only plants (3 countries), or only on plants and animals (2 countries). All 29 of the countries still consulting on their laws, including the EU countries, are only considering regulation changes for use on plants.

The proposed changes in our gene technology laws does not align us with trading partners. We would open our borders to, or produce within our borders, unregulated outcomes that our trading partners regulate.

- Of all countries that have changed their gene technology laws, only Canada and Australia have no mandatory notification requirement (and for Canada, changes are restricted to only plants).
- The United States also limited the number of modifications and their distribution, such as no more than one modification per gene, that could be made to plants that are exempt from GMO regulations.[6] New Zealand could under the proposed Bill have no limitations of this kind.
- Australia but potentially not New Zealand defines the use of SDN2 and oligonucleotide mutagenesis (ODM) as *distinguishable from conventional breeding*.

In short, in at least one significant way, New Zealand proposes to accept risks to human health and the environment unacceptable to any other country.

A statement on medicines

Our submission is not about the use of gene technology in medicine. We are generally comfortable with the proposed legislation for medical research and therapy development. The

[6] https://www.govinfo.gov/content/pkg/FR-2024-11-13/pdf/2024-26232.pdf. Access date 14 January 2025. Note that the December 2024 District Court decision has put even these exemptions on hold.

exception would be for the use of gene technology to produce or alter organisms such as pharma crops or oral vaccines that might only be regulated when converted into a medicine or food.

Our comfort comes from research in other countries on regulatory impact on medical research. That research has not found that gene technology regulations similar to New Zealand's have had a significant effect above and beyond what is normally required for that kind of research [4]. Personnel safety and laboratory containment requirements and documentation for research or commercial reasons is largely redundant with regulations on gene technology.

A statement on socioeconomics and ethics

INBI does not agree that a scientific risk assessment is sufficient information to inform a correct decision on the use of gene technology. The Cartagena Protocol on Biosafety allows a decision-maker to take both socioeconomic issues and a scientific risk assessment into account. Decisions based solely on the biology of an outcome of gene technology are neither based on sound risk assessment science nor appropriate for our complex social and trade environment [5].

The ability of trade partners to detect products of exempt and non-notifiable (and likely unregistered) activities will continue to improve [6, 7]. As this happens, the risk of trade disruptions and lost revenue increases. For example, the exported product could be unmodified but contaminated with trace amounts of undeclared material that derives from the use of a gene technology on something else. [7] Various jurisdictions, including the European Union and Brazil, have zero tolerance for unknown genetically modified organisms (GMOs) [8, 9].

The science case is not made

Our submission emphasises scientific issues that arise if the proposed Bill passes into law. A scientific risk assessment is an obligation under the Cartagena Protocol.

The extent of the scientific problems require a dedicated submission. In Chapter 1 we discuss the flawed understanding of risk behind the proposed legislation and why that matters. Chapter 2 reviews how the proposed legislation introduces an inconsistency in regulation of different tools used in gene technology, and how that could cause harm. Chapter 3 illustrates how it is scientifically and practically unjustified to expect that any routine use of gene technology would avoid making outcomes described in higher risk tiers. Such outcomes are too common to dismiss from the mix of products and must be purified away from those that are minimal or low risk. Chapter 4 exposes the costs to safety from ending the traditional use of containment for research and development purposes prior to environmental release.

The proposed scheme is not risk-proportionate

A purpose of the proposed legislation is to create a better framework for ensuring that "restrictions on gene technology and GMOs is proportionate to the risks that each application poses." [8] We believe that the proposed framework would not be risk-proportionate [10].

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[7] To give an indication of how complex the issue is, the United States does not exempt the following: "A GE organism is subject to regulation if it is a plant that has not been evaluated for plant pest risk; or an organism that meets the definition of plant pest; or is not a plant but has received DNA from a plant pest, and the DNA from the donor organism is sufficient to produce an infectious entity capable of causing plant disease or encodes a compound that is expected to cause plant disease symptoms; or is determined by the Administrator likely to pose a plant pest risk." https://www.regulations.gov/document/APHIS-2018-0034-6194 Access date 20 January 2025.

[8] Quote from RIS.

It is not possible to ensure that described *exempt and non-notifiable activities* will be free of outcomes that fall into notifiable, high risk, categories. This Bill would liberalise the law but would not maintain adequate protections for human health and the environment.

Modification to the status quo process-based framework would be less onerous to enact and less likely to result in harm to human health, environment or animal welfare, providing a superior alternative to the proposed scheme. A modification of the status quo could continue to require that activities are contained but provide, if appropriate, for expedited release of products demonstrated to conform to exemption criteria or conditions of a risk assessment.

Chapter 1. Confusion of hazard, risk, and role of regulation in biosafety risk assessment

- GM organisms are hazards not risks. How, where, and by whom they are used is information needed to determine how the hazard becomes a risk of harm. A priori exclusion of some gene technology processes from legislative scope, notification, or licensing requirements is not scientifically justified on a consideration of them only as hazards or in comparison to hazards created by conventional breeding.
- The Bill is over-reliant on experience with a very narrow range of biodiversity and particularly individual plant species.
- The chemical and biological vectors of gene editing and gene silencing tools are also hazards (Chapters 1 and 2) and this proposed legislation fails to responsibly regulate the risks they create.
- Solution: require the use of certified containment facilities for all uses of gene technology and release only products demonstrated to meet exemption or release criteria (i.e. following risk assessment).

Beginning with chemical and radiation mutagenesis in the 1930s to the present, gene technology risk has been mitigated by regulatory requirements that the use of gene technology was restricted to containment facilities. Living materials, from viruses to cells to multicellular organisms, are exposed to gene altering agents within facilities designed to prevent unintended exposures, and prevent release into the environment of potentially hazardous GMOs or mutagens.

The RIS implies that chemical and radiation mutagenesis are conventional techniques by conflating a historical decision of expediency to regulate the reagents instead of the GMOs that these tools create. [9] Conventional breeding is instead "selective breeding" or "traditional breeding", a fundamentally different biotechnology from gene technology because it is not a means to increase mutation rate (see Chapter 3).

All gene technologies increase the de facto mutation rate [11]. The subtle conflation of chemical/radiation mutagenesis with selective breeding (mis)leads the reader of the Bill to the conclusion that risks created from the use of chemical and radiation mutagenesis define what is acceptable to society.

Hornets' nests are more than the sum of their hazards

It is tempting to follow the simplistic logic behind a call for product-focussed regulation, with stringency proportional to risk. However, this legislation does not achieve even that because the GMO is neither the risk nor the appropriate focal point upon which to tier it.

The GMO is a potential *hazard* made through gene technology. A hazard becomes a risk when it has the opportunity to cause harm. That harm might be to human health or the environment. In other words, how human beings or the environment are exposed to the hazard determines its potential to cause harm.

The list of gene technology hazards includes the intended modified organism, any unintended modifications of the intended modified organism, organisms modified unintentionally, and potentially harmful chemical or biological formulants/vectors. Under the proposed legislation wherein development, containment, notification, and release requirements are relaxed, the process itself is also released from containment and therefore from controlled and anticipated exposures.

[9] E.g. RIS paragraph 131 "Organisms that are developed using specified non-regulated techniques that modify the genetic makeup of an organism, including conventional techniques such as selective breeding or chemical mutagenesis, are not subject to regulation as GMOs."

Hornet sting risk assessment matrices (Figure 1) illustrate the error of extrapolating risk from a description of a hazard. The individual idealised product of gene technology may be a hazard even if that hazard could have arisen by other (unregulated/spontaneous) means. However, the use of gene technology may alter the likelihood or context of exposure to the hazard.

A nest of hornets each of equal hazard can be more harmful than a rare one (Figure 1A). The risk varies for a nest close to a home depending on presence of children (Figure 1A) and those with an allergy to venom (Figure 1B). The Bill collapses risk to a scientifically unjustified comparison of hazards.

The risk assessment would necessarily be different when the modified organism was a crop plant, plant pest, flea on a house pet, virus in a chicken, or a bacterium common in earthworms, because each would have very different environmental contexts, release numbers, and ways in which human and animal health or the environment might be harmed. The Bill fails to manage this complexity and the effects of uncontrolled entry into the environment of non-target organisms that have unintentionally been modified.

Context cannot be ignored in risk assessment

Context-dependent gene technology activities and how resulting products are used can be unlike anything resembling conventional breeding even if in theory both processes could make the same product.

Image created using DALL·E by OpenAI

> CRISPR is not only limited to traditional laboratory contexts with academically trained scientists or in the field as a gene drive. Community laboratories and DIY bio enthusiasts (also called "biohackers") are using the technology…Kits available online appear to actively market to those in DIY bio spaces, sometimes disparaging the "traditional" science laboratories from which this technology was developed, in many cases to make biological science more accessible for those not in traditional science careers. One of the more well-known companies is Odin, founded by Josiah Zayner, a well-known and controversial proponent of citizen science. Zayner's biotechnology supply company has expanded in recent years to include kits for the genetic manipulation of a wide variety of organisms, including plants and animals. One kit sold on the site is for genetic modification of tree frogs, with a CRISPR insertion that increases expression of a growth hormone and consequently increases the size of the frogs. [12]

The above example provides some insight into the broad and unpredictable range of ways that exempt activities might be used, and by whom. We are unaware of conventional tree frog breeding efforts of similarity to livestock and crop development. No tree frogs are listed on the International Atomic Energy Agency list of organisms modified using chemical or radiation mutagenesis. The conventional breeding standard is non-sensical in the many contexts that would be made possible under the proposed law.

However, were large tree frogs a benefit for conservation or environmental reasons, scientists could still make them using gene technology instead of breeding. Ensuring that the frogs were developed in containment facilities that operate ethically would not prevent the intended frogs from being released into the right environment.

Beyond the intended target of the gene technology treatment are the hazards arising when: 1) other organisms, including people or pets, are purposely or inadvertently exposed -

Hornet Risk Assessment

LOW, LOW MEDIUM, MEDIUM, MEDIUM HIGH, HIGH

Severity of harm

Likelihood of harm	Negligible	Minor	Moderate	Significant	Severe
Very likely					
Likely					
Possible					
Unlikely					
Very unlikely					

Hornet Risk Assessment

LOW, LOW MEDIUM, MEDIUM, MEDIUM HIGH, HIGH

Severity of harm

Likelihood of harm	Negligible	Minor	Moderate	Significant	Severe
Very likely					
Likely					
Possible					
Unlikely					
Very unlikely					

Figure 1A. Risk vs Hazard Assessment

Each matrix illustrates two risk assessments based on the same hazard, a hornet. Comparisons between the number of hornets (top) or likely exposures (bottom) show that the outcome of a risk assessment differs significantly from the same hazard depending on context.

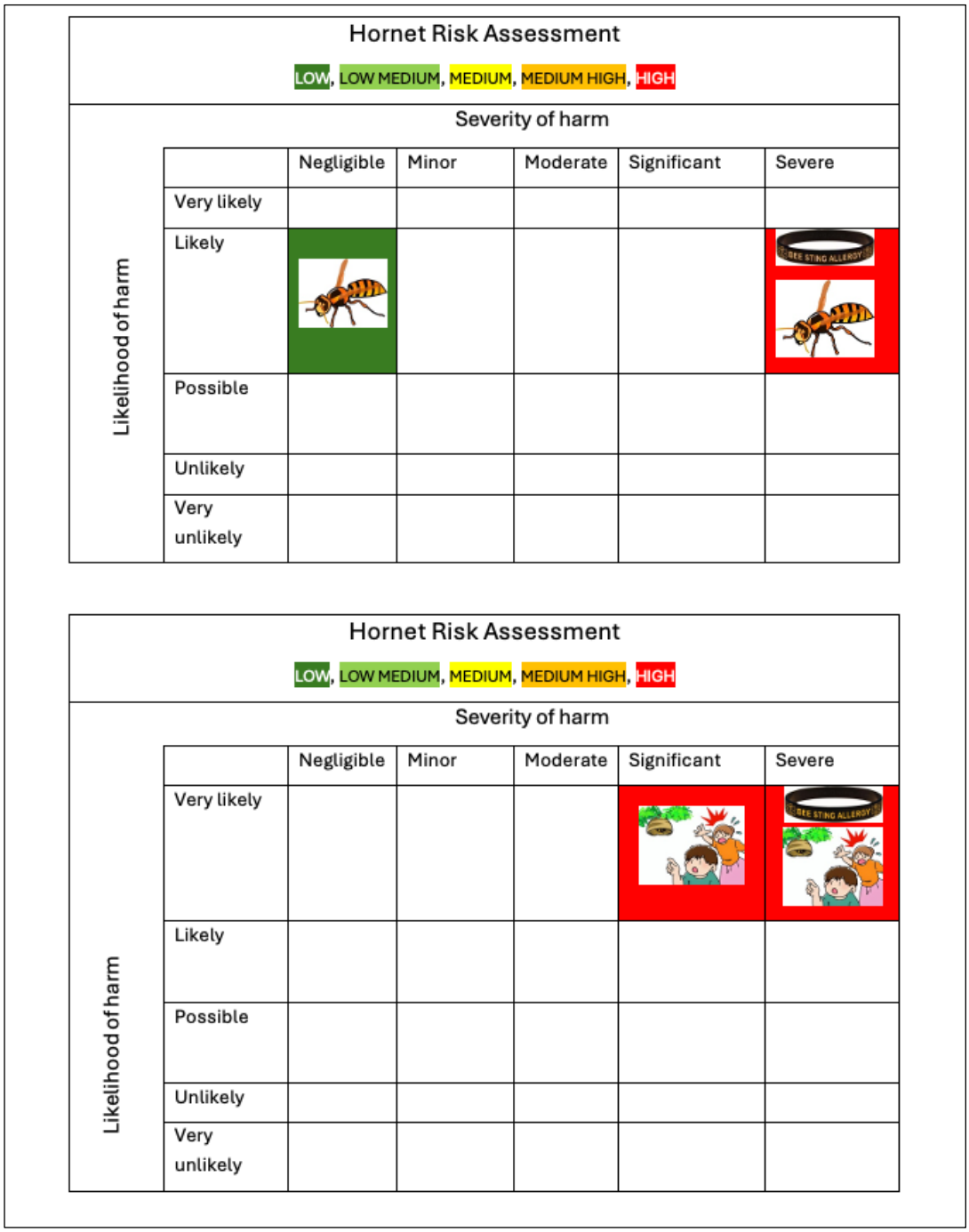

Figure 1B. Risk vs Hazard Assessment

The indistinguishability of the hazard does not determine risk. In both the top and bottom panels, the essential element is whether someone with a bee sting allergy (indicated by bracelet) could be exposed. Indistinguishability of hazard also does not make either risk scenario acceptable (bottom panel).

> [W]e developed an at-home CRISPR editing kit that we shipped to over 600 enrolled students during the remote offerings of the course from Fall 2020 through Spring 2021…Regarding challenges with the kit, a few students commented that it was hard to find appropriate space in their shared accommodations… [13]

or 2) pathogens are altered but not killed by exposure -

> Another example of a biohacker using themselves to experiment is that of Aaron Traywick, who injected himself with CRISPR targeting herpesvirus at a Facebook-broadcast event. [12]

Various chemicals, radiation, and gene editors (even if applied narrowly in defined reactions such as SDN1 and SDN2) are powerful mutagens (Table 1). The hazard of using chemical and radiation mutagens is mitigated by regulatory controls that control access, intensity/concentration, and require use in certified facilities that limit exposures and ensure that any unused mutagen or unwanted products (intended or unintended targets of the technology) are properly tracked through to responsible disposal. Despite their powerful mutagenic properties, the proposed legislation would treat the combination of biological/chemical vectors used for gene editing and the gene editors themselves (e.g. CRISPR/Cas, ZFNs, TALENs) differently to other powerful mutagens by excluding some uses from legislative scope or notification requirements.

Ex ante assessment is not scientifically justified

The proposed legislation also replaces scientifically valid risk assessment with an anti-scientific ex ante assessment that all possible future exposures to these tools and vectors has been anticipated and results in acceptable risk to everyone and in every environment. The United States National Academies of Science and Medicine (NASEM) rejected ex ante approaches. For example, in its 2016 report on GM plants it said:

> One can imagine an argument being made by certain stakeholders, that if the U.S. government found a plant to be safe, that judgment should be good enough for a country without the resources to conduct its own environmental analysis. That would be wrong. [14]

In other words, the *risks* of gene technology are dependent on where, how, and for what reasons it is used [12, 15]. The proposed ex ante risk assessment incorrectly substitutes hazard assessment. Organisms made by gene technology may have the potential to create categories and sizes of exposures that organisms isolated in conventional breeding processes never achieve.

> Due to the technical characteristics of [New Genomic Techniques] [10], the sites of the unintended changes, their genomic context and their frequency (in regard to specific sites) mean that the resulting gene combinations (intended or unintended) may be unlikely to occur with conventional methods. [16]

On this point it is worth noting that a US Court has struck down an earlier decision to amend gene technology regulations. This has two implications for the present situation here. First, it challenges the impression that our major trading partners are moving in only one direction. Second, the Court found the reforms invalid because they were based on the same flawed scientific reasoning being used to promote the gene technology bill.

The NASEM conclusion from the 1980s that "the genetic engineering process, per se, presents no new categories of risk compared to conventional breeding" is a critical part of the logic-gone-awry behind reducing the requirements for contained development and assessment of products prior to release. NASEM may also have said this about uranium atoms used in nuclear reactors or bombs. Indeed, spontaneous fission chain reactions lasting a few hundred

[10] The term Europe uses as the rough equivalent of Australia's New Breeding Techniques and the terminology used in the proposed legislation s163(2).

thousand years occurred in Africa around 2 billion years ago. It might therefore be said that using nuclear technology introduces no new *category* of risk.

NASEM was unlikely saying that. Africa 2 billion years ago had no people. Earth may still have had no multicellular organisms. The conditions of exposure were alien to anything we might take into consideration for an outdoor nuclear fission reaction now.[11]

While NASEM expressed confidence that the products of gene technology were not inherently unsafe, they were also not saying that they were inherently safe, or as safe as every product of conventional breeding. The distinction is revealed in how NASEM described its reluctance to extend ex ante assessment to food derived from GM plants.

> There are many reviews and official statements about the safety of foods from GE crops (for example, see Box 5-1)…With regard to the issue of uncertainty, it is useful to note that many of the favorable institutional statements about safety of foods from GE crops in Box 5-1 contain caveats, for example: 'no overt consequences,' 'no effects on human health have been shown,' 'are not per se more risky,' and 'are not likely to present risks for human health.' Scientific research can answer many questions, but absolute safety of eating specific foods and the safety of other human activities is uncertain. [14]

Hazards can be indistinguishable and unacceptable

Emphatically, NASEM did not endorse the idea that because a product of conventional breeding could be very harmful in some contexts that all products of any use of gene technology should be exempt from risk assessment prior to release. It isn't just that nature or conventional breeding could plausibly make something undesirable to human health or the environment, it is that without technology those things happen at profoundly lower frequencies and in fewer locations where they can cause harm.

Federal Judge Denato captured this when he said:

> The 2002 NAS study acknowledged that "[i]n the 1980s . . . an assumption was made that, even though conventionally bred crops were not considered to be completely risk free, the risks associated with the entire class of crops should be considered 'acceptable' to society."…It concluded that "the assumption that all conventionally bred crops have 'acceptable risks' is not scientifically justified" and therefore "[t]he risks associated with crop cultivars that have been or could be developed through conventional breeding should not be assumed to be acceptable."

Failure to regulate a hazard created by one kind of technology, conventional breeding, is not an excuse to ignore a hazard created by another, such as gene technology. To the rejoinder that it is not absolute but relative risk that is used as the comparator, Judge Denato said:

> But that contention still takes the risk from conventionally bred plants as the baseline on which the scope of regulatory oversight should be defined, a premise the 2002 NAS study concluded is "not scientifically justified"…

[11] A similar argument by MK Hansen: "One could argue that synthetic chemicals are just an extension of basic chemistry, and in certain senses they are. Yet when we began creating new chemicals that had not previously existed on the earth, or which had only been present in small quantities, and began distributing them massively, we discovered that many of these chemicals, even though they were made of the same elements as 'natural' chemicals, had unexpected adverse properties for the environment and health. Because we had not co-evolved with them for millenia (sic), many (though by no means all) had negative effects. Among the serious problems were PCBs and vinyl chloride, which were found to be carcinogens, and numerous organochlorine pesticides, which were found to be carcinogens, reproductive toxins, endocrine disruptors, immune suppressors, etc" https://advocacy.consumerreports.org/wp-content/uploads/2013/02/Wide-Crosses.pdf Access date 29 December 2024.

Table 1. Comparison of mutation power and other characteristics

Cause	Mutation frequency	Reference
Spontaneous banana	<0.000000006.	[17]
Spontaneous algae	0.0000001	[18]
Spontaneous thale cress	0.0000002	[19]
Chemical (EMS) mutagenesis banana	0.00002	[17]
Chemical (EMS) mutagenesis tomato	0.000003	[20]
Gamma irradiation tomato	0.0000004	
SDN1 (ZFN) tobacco	0.05	[21]
SDN1 (CRISPR/Cas9) rapeseed	0.65 (range 28% to 100%) (up to 21% of plants had a mutation in each copy of the same gene)	[22]
SDN1 (CRISPR/Cas9) tomato	0.68 (range 14-100%) (52% had a mutation in each copy of the gene)	[23]
SDN1 (CRISPR/Cas9) tomato targeting 3 different genes at once	0.25	
SDN1 (Cas9 vs Cas12a) tomato	Up to 0.34 (mean=13%) with variant LbCas12a Frequency of off-target (1-2 mismatches) at predicted sites 10/55=18% Cas9 off-target 0.07 with up to 3 mismatches.	[24]
SDN1 ("PAM relaxed" Cas9) rice	0.15-0.2 at target (using SpCas9-NGv) 2 plants examined using whole genome sequencing. 12 off-target mutations, 6 off-target mutations in each plant, 5 of 6 common to both plant genomes	[25]
	0.4-0.6 at target (using SpCas9-NG) 2 plants examined using WGS. 11 off-target mutations. 5 were different between the two examined plants.	
Base editor ("PAM relaxed" Cas9) rice	0.3-0.45 at target (nSpCas9-NG-PmCDA1) 2 plants examined using whole genome sequencing. 12 off-target mutations, 6 in each plant. None were in common between the two examined plants.	[25]
Cas9 with phage λ red recombination *Escherichia coli*	0.26 off-target frequency, probably due to error-prone polymerases induced by Cas9 activity.	[26]

This remains the view of the US National Academies. In their 2016 update on gene technology applied to plants, NASEM said:

> In many cases, there may be substantial uncertainty about whether there is a hazard at all or how severe the hazard is. As technology provides plant breeders with more powerful tools, it creates the

> potential to introduce novel traits with which breeders and regulators have no clear comparators or experience. Such cases may be rare, but given the potential for novel exposure, it is a reasonable policy response to review such plants before their release into the environment. Risk managers can obtain additional information under field trial conditions requiring containment and other risk-mitigation measures intended to prevent uncontrolled releases." [14]

One final observation is that the proposed legislation would excuse developers and the regulator from a responsibility to assess the risk of organisms of **any species** based on the presumption that the changes made by some techniques are indistinguishable from conventional breeding. Yet most species have never been bred conventionally or otherwise, and provide no baseline for comparison. Only a relatively small number of plants have been bred for use as crops and industrial feedstock, and animals for livestock or feedstock, fungi and bacteria for mainly secondary products.

Australia also exempted fungi, bacteria, and non-agricultural plants and animals, on the supposition that use of gene technology can create outcomes indistinguishable from conventional breeding. Yet it curiously defined conventional breeding as "A traditional method of developing new traits in plants or animals not involving gene technology" [27]. Aligning our regulations with a questionable use of conventional breeding by Australia is scientifically unjustified.

The legislation uses a yardstick that would not apply to the vast majority of life that might in the future be purposely or unintentionally exposed to gene technology, and the presently unimaginable combinations of uses, combinations of organisms, and variety of places in which they may be used.

For instance, antibiotic resistance arises by spontaneous processes in nature. Very small changes in genes can lead to antibiotic resistance. Conventional culturing of bacteria can be used to "breed" antibiotic resistance. Yet this does not make the risk of using gene technology to spread antibiotic resistance in bacteria in hospitals or chicken pens acceptable to society.

Regulatory reform instead should be based on scientifically justified premises. The meaning of "proportional to risk" should be articulated such that it can be measured, with clear and testable endpoints for ensuring that risk, not just hazard, is acceptable. In our view, this is too much to leave to secondary legislation.

Chapter 2. The techniques proposed to be excluded from scope would create a regulatory and safety inconsistency

Key points

- Just as using chemical and radioactive mutagens carries significant risks, the use of gene technology tools poses inherent risks. Chemical and radioactive mutagens are regulated and biological products derived from their use are registered with the International Atomic Energy Agency. Comparable regulation should apply to all gene technology tools.
- In many ways gene editing and similar tools are even more effective and efficient mutagens, but they would become unregulated as mutagens and as processes that produce regulated organisms.
- Solution: require the use of certified containment facilities for all uses of gene technology and release only products demonstrated to meet exemption or release criteria (i.e. following risk assessment).

Chemical and radiation mutagens (see Appendix 2) are arguably natural and create outcomes that may be indistinguishable from those that arise spontaneously in conventional breeding, but these tools are used at unnatural concentrations and exposures that can cause harm to users or the environment and can create harmful organisms. Chemical and radiation-based gene technology is comprehensively regulated despite them being by some measures approximately 1000-10,000 times less potent than gene editing and silencing tools (Table 1).

The proposed legislation would inconsistently remove effective regulation of mutagens provided that they involved site-directed nucleases or nucleic acid oligomers (e.g. ODM), or where chemical or biological vectors used in gene technology.

There are no natural analogues to the tools used in gene editing. The site-directed nucleases (SDNs) are either synthetic mutagens (e.g. ZFNs, TALENs) or are alien proteins in most species (e.g. CRISPR/Cas) including all plants, animals, and fungi. In other words, most of the species that would be modified intentionally using these mutagens would effectively never be modified by a similar process through conventional breeding or in nature.

Analogous mutagens are regulated. Chemical and radioactive mutagens are tightly controlled, must be used by trained personnel in proper facilities, and are tracked through to disposal. Yet they potentially make organisms indistinguishable from conventional breeding.

Gene technology involves many hazardous agents. Gene editors and other “biological” mutagens become hazards when combined with emerging chemical or biological delivery tools [28, 29]. These tools are engineered biological or chemical vectors that carry the mutagens into living cells.

Vectors are potentially harmful agents with ongoing and rapid development. The applications of formulations composed of emerging vectors and gene editing tools cannot be assumed to create risks indistinguishable from conventional breeding.

Even if it were possible someday to expect gene editors to produce only products that were indistinguishable from those developed in conventional breeding (see Chapter 3), for the foreseeable future it is not possible to exclude other potentially harmful or heritable effects on any organism intentionally or unintentionally exposed to the vectors.

The same considerations apply to the use of chemical and radioactive mutagens as to biological mutagens, such as CRISPR/Cas. These considerations are well known as the following quote from 1949 illustrates:

> The general methodological requirements for work with chemical mutagens are the same as for general mutation work, with special emphasis on questions of concentration, penetration, possible

> indirect or delayed effect, differences in susceptibility between individuals, strains and species. [30]

Variables include the effectiveness of the mutagen, the species exposed, the tissue of the organism used, and the duration of exposure [31].

> The activity and fidelity of gene editing is heavily affected by the expression level and duration of the editors in the cells. Therefore, methods to deliver Cas9/sgRNA into the target cells profoundly influence its off-target effect. [32]

For all the above reasons, the most responsible approach is continued regulation and containment of all techniques of gene technology until a purified and verified modified organism is ready to be released. It would not be responsible to remove some processes and products from legislative scope based on present uses and vectors.

Chapter 3. No use of gene technology creates only products indistinguishable from conventional breeding

Key points

- The Bill does not adequately preserve the benefits that containment has made to ensuring that products of gene technology are safe.
- All techniques proposed to be excluded from the GMO regulations or notifications frequently *unintentionally* produce organisms that are in the contained and notifiable tiers.
- Without regulation to ensure that the product is free of transgenes, expect that they will not be free of transgenes.
- The Bill is over-reliant on experience with a very narrow range of biodiversity and particularly individual plant species.
- Solution: require the use of certified containment facilities for all uses of gene technology and release only products demonstrated to meet exemption or release criteria (i.e. following risk assessment).

Conventional breeding is a biased and undefined process

The determination of whether a process or product falls within legislative scope and if it does, whether it is notifiable or should benefit from a risk assessment prior to release hinges on an intangible similarity to outcomes achieved by conventional breeding (or spontaneous natural occurrence).

The term "conventional breeding" is another example of the import of concepts primarily from agriculture and most particularly from plant biology into the proposed regulatory framework [33]. The UK Royal Society definition of conventional breeding is a classic example.

> Conventional breeding achieves [the goal] by crossing together plants with relevant characteristics, and selecting the offspring with the desired combination of characteristics, as a result of particular combinations of genes inherited from the two parents.

The United States uses conventional breeding as a comparator. It too acknowledged that the standard has different interpretations [34].[12] However, unlike in this proposed legislation, the US limited the conventional breeding standard to plants. Most countries limit their regulatory reform to plants which are most likely to have a history of conventional breeding [35].

The standard as described by the US is illustrative. The conventional breeding standard for an exemption using techniques of gene editing is based on: 1. the low frequency of off-target mutation relative to total mutations spontaneously arising without use of gene editing; and 2. that plant breeding allows for segregation of unintended changes [p. 29793 of ref. 34]. As can be seen in Table 1 (Chapter 2), the first standard is not evidently satisfied in plants if you compare frequencies of mutation in genes that are relevant to an intended outcome. Segregation is applicable only to certain kinds of organisms that depend on meiosis for reproduction and does not apply even to all kinds of plants, animals, or fungi and does not apply at all to bacteria. Therefore the standard is not transferable to the range of species proposed in the New Zealand gene technology bill.

The history of conventional breeding in crop plants provides some argument for exempting defined activities on plants but is nevertheless not a scientifically justified standard for ex ante risk assessment. It was rejected by a US Court as a foundation for reforms in the US gene technology legal framework.

[12] "Other Federal or State regulations may use the term 'conventional breeding' in the context of their regulations and attribute slightly different meanings."

The are many problems with this comparison. First, there is limited knowledge of the range of outcomes that could arise from most species, because conventional breeding experience is concentrated in a small number of crop plants [36] and perhaps some species of livestock.

Second, it is unclear when the comparator includes organisms developed using mutation breeding using chemical and radiation sources. The UK Royal Society definition does not mention such tools in its definition,[13] the scientific literature is mixed, and the US NAS and RIS do. Including mutagenesis breeding within conventional breeding artificially expands the range and rate of production of potential hazards, further stretches scientific credulity and public trust of the regulatory system.

For example, it at first seems impressive that over 3400 plant varieties[14] have been created by chemical or radiation mutagenesis and released for use in agriculture over the last 100 years. The familiarity and scale implies that mutagenesis breeding has become conventional and has a track record of safety. Revealing that 60% are from just 6 plants – rice (876), barley (309), chrysanthemum (288), wheat (276), soybean (184), and maize (89) – and the next largest group of 4 plants – groundnut (79), common bean (57), cotton (48), and mung bean (43) – contribute only 7%, with over 52% created only since 1990, paints a picture of very limited experience with mutagenesis breeding.

Outcomes of chemical and radiation mutagenesis are not suitable comparators because in contrast to selective breeding they are a technology intended to magnify variation at the genome level. The extreme outcomes of these tools are not indicative of the frequency or probability of harm from selective breeding or spontaneous mutations in nature [2, 31].

Third, how the organism or its tissues is exposed to the mutagen influences the outcome. Such variables are controllable when the mutagen is used in a containment facility, as are chemical and radioactive mutagens. To the degree that they are not controllable, the product is still contained and may be destroyed if necessary.

Finally, as noted by the US Department of Agriculture Animal and Plant Health Inspection Service (APHIS), uses of SDN1, SDN2, and each or both in multiplex or sequential reactions, can create outcomes with no known equivalent in conventional breeding.

> We have not yet identified any literature demonstrating that identical indel or deletion modifications can be achieved across subgenomes using conventional breeding methods. For this reason, we are restricting the application of AM2 in combination with AM1,[15] when a repair template is used, to allow modification to one pair of homologous chromosomes.

The point the US makes about scalability is also illustrated in Table 1, above. For these and more reasons, the use of "distinguishability" from outcomes achieved on very different time scales and frequencies is not suitable as a benchmark to dismiss the comparative risk of an organism made using gene technology.

Gene editing techniques such as SDN1, and even perhaps SDN2, occasionally create products that could arise from conventional breeding, just as do chemical and radiation mutagenesis. However, they cannot be relied upon to do so at any time much less all the time. To illustrate we will discuss some of the many ways in which that outcome is a lottery.

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[13] Even the industry organisation ISAAA makes a distinction between conventional breeding and mutation breeding. https://www.isaaa.org/resources/publications/pocketk/13/default.asp Access date 29 December 2024. "Mutation Breeding. In the late 1920s, researchers discovered that they could greatly increase the number of these variations or mutations by exposing plants to X-rays and chemicals."

[14] 3460 in the Mutant Variety Database of the IAEA as of 16 January 2025.

[15] According to US §340.1, AM1 is a combination of SDN1 and SDN2 categories and AM2 is multiplex or sequential modification.

Recall from Chapter 2 that newer tools for gene technology have hugely improved efficiencies. At their present efficiencies, multiple changes in the same genome are unavoidable. Sometimes this is the point, as in serial or multiplex reactions intended to incrementally advance the divergence of the DNA sequence from the original, or to cause mutations in many different related or unrelated genes of an organism all at once [37]. Over a hundred changes have been made at one time [38].

Besides bearing no resemblance to conventional breeding, the power to create change like this also raises the frequency of unintended changes. For example, when SDN1 reactions were applied to the tomato genome, intended modifications occurred at a frequency of about 50% (half of the exposed plants were mutated at the defined place [24]. That is a massive increase in efficiency compared to any previous technique of gene technology. The efficiency of mutation at unintended places in the genome was also highly efficient, with about 25% of exposed plants having unintended mutations. The overlap between plants with intended and unintended was also extremely high. Essentially *all plants that had unintended changes also had the intended change*, meaning that amongst the hundreds or thousands of intended products made in these processes, half had unintended changes.

The response to these facts may be that even unintended changes are indistinguishable from conventional breeding. That response is vague, anecdotal, and subject to endless challenge, conflating rare and extreme outcomes in conventional breeding to routine outcomes using gene technology (see Chapter 4). It is also incorrect. One reason that it is incorrect is the focus in this chapter: how those unintended sites of DNA damage frequently result in the unintended integration of transgenes, which if intended would be regulated at higher risk tiers.

SDN1/2 reactions produce outcomes distinguishable from conventional breeding

Transgene insertion through the routine use of gene technology is unavoidable. The use of genome editing techniques is unlike conventional or mutation breeding because they always involve exogenous sources of contaminating genetic material. DNA/RNA contaminants are used by cells to repair the damage caused by the site-directed nucleases regardless of whether or not the genetic engineer wants them to be.

Development of "polled" cattle in the United States illustrates the point. The company Recombinetics developed hornless cattle using SDN1. It then claimed that they were confident of no unintended changes in the cattle genome. As described by the Director of the FDA Center for Veterinary Medicine which later found multiple transgenes:

> This edit was designed by [Recombinetics] to produce an alteration mimicking a sequence "found in nature." This characterization of the alteration is significant because some policymakers and scientists have argued that using genome-editing techniques to replicate a 'natural' mutation should not be of regulatory concern because it is equivalent to existing, naturally occurring alleles. FDA's (our, we) analysis illustrates, however, why it is necessary for there to be regulatory oversight of intentional genomic alterations in animals, even when the intended modification seeks to replicate a naturally occurring mutation…The unintended alteration in this case resulted in the integration of a bacterial plasmid containing various sequences designed for use in molecular biology, including antibiotic resistance [genes]. [3]

A guiding principle in science is that 'absence of evidence is not evidence of absence'. Where and how you look for these outcomes influences what you find. For example, the FDA discovery of bacteria DNA in the genomes of gene edited cattle was attributed to how the developer chose to look for off-target changes [39]. The polled cattle are not a rare exception to the rule. Using whole genome sequencing, five unintended large insertions of biological vectors were detected in the genome of gene edited oilseed rape [40].

> …current sequencing-based genotoxicity assays, whether directed to specific sites or unbiased, have a technical limit of detection of ~1 in 10 000. Thus, when creating a modified cell population of several hundred million cells, even with the most sensitive sequencing-based assays, there could still be tens of millions of cells that have undetected nuclease-induced off-target mutations and rearrangements. [41]

The take home lesson from these examples is that outcomes indistinguishable from conventional breeding are only true when they are proven to be [42]. Fonterra have consistently made this point as well. The second lesson is that the standard of proof must be set by law, not developers, and must evolve as the technology evolves.

Gene technology tools are always contaminated with genetic material from multiple species

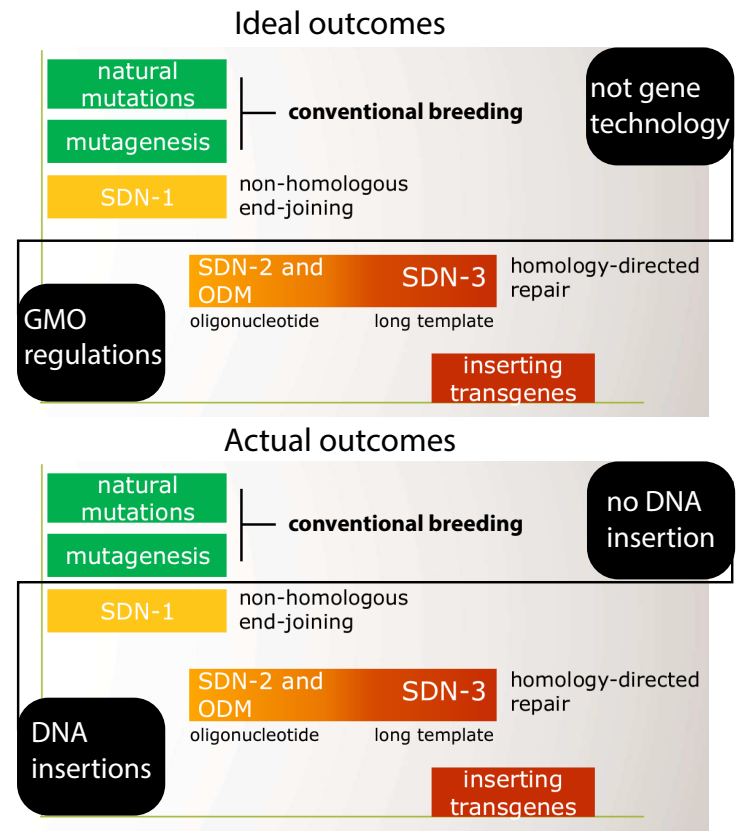

Figure 2. Idealised outcomes of gene technology behind the Australian regulations (top). Actual transgenic outcomes of different techniques of gene technology from unavoidable DNA contamination and sequential or multiplex (e.g. SDN2) reactions (bottom).
Graphic modified from https://www.ogtr.gov.au/sites/default/files/files/2021-07/foi-021-2018_0.pdf.

How do genomes grab transgenes even when transgenes have not been purposely introduced? The answer is that reagents (necessary ingredients) used in these reactions have biological origins and all the different components - and there are many - have *inseparable* contaminants. A second source is contamination with DNA during the use of these reagents. Either source of contamination can and does unintentionally produce the intended outcomes of SDN3 activities (distinguishable from nature and conventional breeding and potentially high risk) through SDN1/2 activities [16, 43, 44] (Figure 2). These outcomes can only be avoided by sorting through the many different modified cells or regenerated organisms after the use of gene technology.

Commercial grade gene editing materials such as the guides (CRISPR) synthesised to work with the site-directed nucleases (e.g. Cas9) are contaminated with other guide fragments [45]. These contaminants might direct the SDN to unintended targets in the target species, or to targets in unintentionally exposed organisms should the technique be exempt from containment requirements. They are also potential transgenic material for insertion into the target genome.

In the above example of commercial grade materials, they were contaminated with fragments of DNA that had sequences found in animals, fungi, plants, and bacteria and specifically mice, fish, flies, yeast, thale cress, and *Escherichia coli*. They also found fragments of DNA from the pipeline of production of the ingredients for a gene editing reaction.

Strikingly, they found DNA fragments that matched SARS-CoV-2 (Covid-19) and human immunodeficiency virus (HIV). They attributed some of the contamination to the DNA synthesising machines [45].

The implication is that future exempt organisms may carry transgene insertions from whatever happened to be of interest to the previous customer of the DNA synthesisers. While the technology of reagent purification can also be expected to improve over time, the potential for other sources of contamination, e.g. user error, cannot. This is especially true if the use of some gene editing techniques is exempted and therefore also the standards of reagents and practitioners is outside of regulatory control.

Removing genetic material requires expensive and often toxic additional treatments and is labour intensive. Even the most stringent attempts to remove proteins and nucleic acids from medicines fail [46]. It is done with some degree of success in forensic police work and ancient DNA research laboratories where there is no other option [47]. Extending this kind of extreme stringency and testing to routine use of gene technology likely would be more expensive and burdensome than to require containment of processes and products of gene technology through development and until products can be shown to meet exemption criteria.

It follows that there is no basis to assume that any use of gene technology will only create the idealise products indistinguishable from conventional breeding [36]. A few examples below from the recent literature demonstrate the risk of developing law and policy from superficial descriptions of gene editing reactions.

> The insertion of foreign DNA has been reported even in case of allegedly 'DNA-free' techniques…For instance, *E. coli* DNA from bacteria used to multiply plasmids, or mammalian DNA from fetal serum added to culture media. For this reason, in the current state of the art no SDN technique can be claimed to be absolutely 'DNA free'. [48]

> Contamination of CRISPR guide sequences was detected in every batch of research-grade oligos procured from all suppliers tested. [45]

> [T]he sheer scale of the contamination is remarkable, and few reagents go contamination free. [49]

> For example, cross-species contamination from bacterial and mammalian DNA has been reported frequently from metagenomic studies. Background nucleic acids are commonly introduced inadvertently by human handling of samples via air, commercial enzymes, DNA extraction kits, Ultrapure-water Systems (UPW) or paper points. Even plain buffer solutions used in metagenomics may be source of foreign DNA. [50]

Chapter 4. Containment is needed to keep risk proportionate

Key points

- The proposed tiered regulatory approach creates disproportionate risk.
- New pathogens can inadvertently be created by exempt/non-notifiable activities.
- Control of DNA synthesis is not a viable risk mitigation.
- Solution: sale of reagents should be restricted to licensed facilities, gene technology should only be used in certified containment facilities, and release only products demonstrated to meet exemption or release criteria (i.e., following risk assessment).

According to the RIS prepared by officials, risk proportionality is better achieved in the proposed "hybrid" process/outcome approach than in either of the other options described as "process" or "product/outcome" approaches.

Proportionality is not carefully defined and outside of mathematics is a derived normative judgement rather than a measurable variable. Proportionality in this case is an assessment of comparative hazards arising from conventional breeding and gene technology outcomes.

Officials extrapolate from hazard to risk to draw the conclusion that:

> This would reflect current scientific understanding that these modifications do not present unique risk to human health or the environment when compared to conventionally developed products. RIS

As discussed in Chapter 1 and illustrated in Chapter 2, the comparators being used include chemical and radiation mutagenesis techniques. If it can be said that mutagenesis breeding has a history of safe use, that history is due to how chemical and radiation mutagens and outcomes of their use have been regulated. Also as discussed in Chapter 1, using as risk comparators the hypothetical, decontextualised, or rare or extreme outcomes achieved by selecting spontaneous natural events through conventional breeding does not reflect the position of the scientific community who are specialists in risk assessment [15, 16, 37, 48].

NASEM found that "[n]ot having government regulation of GE crops would be problematic for safety, trade, and other reasons and would erode public trust" [14]. The tiered approach to regulation it advocated would integrate both *hazard and exposure* criteria.

Process can inform the potential for the organism to have a change that might make it a hazard in some context [51]. NASEM recommended routine use of "omics" techniques to find changes caused by gene technology. Whereas selective breeding can amplify an unintended characteristic, it could not create a mutation or epigenetic change that caused the trait.

An exception arises if mutagenesis breeding is conflated with selective breeding under the heading conventional breeding practice. The RIS frequently conflates regulated uses of chemical and radiation mutagenesis with unregulated conventional breeding processes (e.g. paragraph 131).

For example, the RIS says:

> This assumption is not based on any evidence that gene technologies fundamentally pose more risk to human health and the environment than conventional methods, which can produce a range of unguided changes to the genetic makeup of an organism. Unguided changes can be untargeted large-scale modifications resulting in a new trait and off target effects of a similar magnitude.

Selective breeding does not produce unguided changes or changes in genes. This is the realm of mutagenesis not selective breeding. It can be used to amplify a population from individuals with spontaneous changes, but only gene technology allows people to make genetic change [52]. Furthermore, the size of modification is not a foundation for an ex ante assessment of

harm equivalence between breeding techniques [2]. NASEM, as have many others, dismissed this pseudo-scientific concept when it said that

> even a small genetic change could lead to biologically important alterations of a crop, so it would not be possible to exempt plants with small genetic changes. [14]

Rather than size of change as a predictor, it is the concentration of change at specified (and unspecified) locations by gene technology that creates what would be rare or virtually impossible outcomes without its use [2, 37, 42, 53].

> [I]t is possible to generate genotypes which are highly unlikely to result from natural processes or traditional breeding techniques. As a result, more 'extreme' biological characteristics can be achieved with NGTs in comparison to conventional breeding methods. These can, however, also be associated with more significant 'trade-offs' in comparison to conventional breeding. [52]

Moreover, the nature of the change matters. SDN1 activities have been used to create new chromosomes by splitting an existing chromosome [12]. That also happens in nature, but extraordinarily rarely. For instance, a barrier to fertility in human x monkey matings is that our chromosome 2 is split in the primate genome into two chromosomes. This kind of modification can induce novel speciation events without any change in DNA sequence.

Techniques of emerging scale such as gene editing and gene silencing also create epigenetic changes. These are often casually dismissed on a semantic argument about what we call a gene while ignoring the root source of risk: heritability [35, 54, 55].

Epigenetic changes can be heritable during development and between generations. Epigenetic mechanisms underpin normal growth and development and aberrant effects such as cancers [56]. Moreover, they are difficult to detect and may go under-reported. For example, the use of SDN1 to introduce a mutation in a gene in the human genome resulted in post-transcriptional production of alternative RNAs, which could lead to production of novel proteins [57]. The adverse effects of epigenetic changes are shared by all living things.

The tiered approach described by NASEM differs from the proposed "hybrid" approach (Option 3) in the gene technology bill. Some processes are removed in the latter from regulatory scope or containment requirements because of ex ante assessment that the processes create hazards indistinguishable from what *might* arise through conventional breeding. In addition, nearly all countries that have or are discussing changes in gene technology regulation explicitly require confirmation that the use of gene technology has created the claimed outcome before it is release as a living organism into the environment (see Introduction).

Without an equivalent confirmation step, scalable harm flows to the environment because gene technology creates a larger population of individuals with identical modifications that are automatically released by legislative exemption. Conventional processes require a selection and amplification phase to achieve the same outcome. We discuss one particularly problematic case in the next section.

Loss of genes can make new pathogenic organisms

Most pathogens must be able to survive while not causing disease. Expression of genes that improve their fitness during an infection of a host might reduce the pathogen's fitness at other times. Therefore, virulence genes are often regulated (turned on and off as necessary). Pathogens across the tree of life - bacteria, fungi, protists, and nematodes – regulate the expression of their genes, and they infect organisms across the tree of life including people, companion animals, livestock, and crops.

Mutations in genes that regulate virulence genes can result in "hypervirulent" pathogens [58]. More broadly, loss of some genes, called anti-virulence genes, can result in a speciation event wherein a strain of an existing species begins to evolve as a pathogen [59, 60]. Both genes that

modulate virulence of individual pathogens and those that interfere with the evolution of species into one that causes disease, could be altered on purpose (e.g. for 'biocontrol') or inadvertently by gene technology. New virulence traits can arise in organisms that are not currently considered high risk and may not be regulated through other laws [61].

New combinations of genetic material or new gain-of-function traits arise from either new DNA or gene loss (deletion of DNA). Even exempt activities intended to only delete DNA, such as SDN1, could create new hypervirulent strains [58].

Disease is not the only potentially adverse trajectory for loss-of-function mutants. Organisms are adaptable

> …by rewiring the cell's metabolism, loss of function mutations can provide substantial fitness benefits under many challenging conditions, even cases such as exotic nutrient combinations where some new enzymatic function might seem to be required. [62]

How they adapt will be influenced by where they are. Therefore, the risk of an adverse effect from loss of function mutations can only be evaluated by taking context into consideration (see Chapter 1).

Exempt/non-notifiable activities can unintentionally make new viruses

The high efficiency tools of gene technology, such as gene editors, are unlike other kinds of mutagens because they are non-random. They are guided to a site of activity. Those guides are (hopefully) designed to ignore unintended sites or sites in unintended organisms. As discussed in Chapter 3, even the best of these design approaches is imperfect.

DNA sequences of sufficient similarity to the intended target are identified in DNA databases and guides are designed to match those sequences. Guides may be tested in silico (using bioinformatics predictions) for potential to bind to other locations in the same genome. Provided that this approach is in the hands of competent personnel and followed, it can help to minimise (but rarely eliminate) off-target effects. The proposed legislation sets no standard of training for the design of guides. If the gene technology is used in containment and mandatory confirmation, then organisms with unintended, undesired, or unknown changes cannot be inadvertently released.

A deeper problem is that genome databases are highly biased to the genomes of the relatively few organism and virus genomes that have been sequenced, and the number of individuals of each of these species which have been sequenced [48, 53]. A third to a half of all bacteria species are completely unrepresented in databases [63]. Therefore, when attempting to design guides, it is impossible to know how truly precise they will be. Even in the comparatively low diversity of human genomes, off-target frequencies can vary between individuals [64]. When reporting and containment requirements are relaxed, the gap in database entries becomes a hazard.

Viral genome databases are particularly sparse. Viruses are ubiquitous and the Earth's virome dwarfs all other biodiversity [65-67]. No one imagines a timely elimination of this blind spot.

Because they often reside in cells, viruses may also be modified simultaneously within intended organisms. Indeed, there is commercial interest in using SDN1 as an antiviral therapeutic [68]. Changing the sequence of the virus genome using gene technology can be unnecessary because the damage caused by the genome editor alone can stimulate viral reproduction and recombination [69].

Demonstrations of SDN1 activity efficacy in a pharmaceutical context axiomatically demonstrate the potential for effects of gene technology on viruses in the cells of any exposed mammal, whether or not either the mammal or the virus is the intended target. An excerpt from a patent application describes this:

> The nucleic acid constructs, CRISPR arrays, and optionally templates, and/or protein-RNA complexes of the invention and compositions thereof include those suitable for oral, rectal, topical, buccal (e.g., sub-lingual), vaginal, parenteral (e.g., subcutaneous, intramuscular including skeletal muscle, cardiac muscle, diaphragm muscle and smooth muscle, intradermal, intravenous, intraperitoneal), topical (i.e., both skin and mucosal surfaces, including airway surfaces), intranasal, transdermal, intraarticular, intrathecal, and inhalation administration, administration to the liver by intraportal delivery, as well as direct organ injection (e.g., into the liver, into the brain for delivery to the central nervous system, into the pancreas, or into a tumor or the tissue surrounding a tumor). [68]

The diversity of delivery strategies, e.g. inhalation or contact with mucosal tissues, would create a challenge to control exposures in any environment other than a certified containment facility [15].

But this is only part of the risk assessment. Another consideration is that the non-random process efficiently converts a large cohort of viral genomes all at once. A virus clone can number in the hundreds in a single cell. Unlike in conventional breeding or chemical/radiation mutagenesis, where mutation is random, site-specific techniques have the potential to create a population of potentially disease-causing new viruses in numbers that potentially launch their successful transition into self-propagating infections whether those be in people, animals, crops, fungi, or bacteria.

Containment is the only viable strategy to avoid the inadvertent construction and release of novel viral genomes at numbers that might make them self-sustaining. Certified containment facilities are designed to hold and neutralise unintentionally made biologicals. Nothing short of a requirement that gene technology be used exclusively in containment, as for example India's regulations require, would constitute responsible use.

Cyber and DNA synthesis security

The ability to collapse cost and time barriers for changing genomes is the key difference between gene technology and conventional breeding. Over time, the cost and time barriers reduce due to computer-assisted reagent design [70], commercial availability of vectors [28], and less need for expert training [12, 13, 71]. The outcomes created may be indistinguishable from conventional breeding but any unacceptable hazards amongst them become more probable than by conventional breeding.

> The ability to rapidly modify a genome at relatively low cost compared to previous methods could make CRISPR systems attractive for nefarious actors at all levels, from individuals through nation states. In the realm of biosecurity threats, CRISPR may be misused to create increased-virulence pathogens, neurotoxins, and even de novo organisms. [12]

Common site-directed techniques such as CRISPR/Cas require synthesised genetic material, i.e. DNA or RNA oligonucleotides. These are used to guide the SDN to its target site. In some processes, a second "repair template" molecule may also be used. Officials have indicated that SDN2 reactions should be included in those exempted from legislative scope.[16]

The line between SDN2 and SDN3 is not specified and is left to secondary legislation. In the RIS, officials have recommended that the hybrid approach be coupled to controls on providers of oligomers.

Screening DNA synthesis providers demonstrates that the Government is aware that in excluding some gene technology processes from GMO regulations, and others from containment during development, notification, or creation without a license, it introduces a

[16] https://www.mbie.govt.nz/dmsdocument/29940-regulation-of-gene-technologies-policy-decisions-proactive-release-of-advice-proactiverelease-pdf Access date 1 January 2025.

new potential for harm. For example, the design of SDN guides or repair templates that meet the letter of the law can be applied in ways (e.g. multiplex and serial modifications) that achieve outcomes distinguishable from conventional breeding and which could be high risk [52].

The proposed controls are, however, insufficient to prevent the potential for harm that may arise by accident or by intent in applications by expert or amateur users of gene technology.

Neither the requester nor the DNA synthesiser may know that the request is for use on a pathogen.

> It should be hard — exceedingly hard — to obtain the synthetic DNA needed to recreate the virus that caused the deadly 1918 influenza pandemic without authorization. But my lab found that it's surprisingly easy, even when ordering gene fragments from companies that check customers' orders to detect hazardous sequences. [72]

Genomic databases are far from being comprehensive repositories of genomes, can be biased against rare organisms and viruses, be unavailable (as for example when privately held), and disappear because of loss of funding [73]. Public and private databases can be compromised [70].

DNA synthesis technology is not static. Just as gun manufacture using 3D printing has made it difficult to both control making guns and the materials of which they are made, leading to more environments where they go undetected prior to use, so too will DNA synthesis.

> [W]e aim to propose a concept and strategy of "printing chemistry" to expand novel applications of printing technology in various chemical processes, including synthesis, analysis, screening, and manufacturing. In this mini-review, we summarize the research progress of microchip-based high-throughput oligonucleotide synthesis based on inkjet printing. [74]

Present commercial suppliers of synthetically constructed DNA templates cannot be assumed to be effective gatekeepers for long.

Summary thoughts for the Select Committee

Processes capable of creating similar hazards need not create similar risks

A sound scientific case for the reforms to gene technology law specified in this Bill is not made. It is still an active area of science to determine if the spectrum of changes wrought using gene technology is ever indistinguishable or equivalent to those arising spontaneously or induced by chemical or radiation mutagens [37, 52, 75]. Gene technology is so powerfully efficient that it increasingly relies on fewer steps between mutation and amplification of mutant populations, the latter being selective breeding, skipping an important risk mitigation step in the breeding process [40].

The Bill and its underlying RIS rely on idealistic and unrealistic outcomes of gene technology. No technique of gene technology can be forced to make outcomes indistinguishable from conventional breeding. Outcomes indistinguishable from conventional breeding, or at least conforming to desired specifications, are identified and segregated away from unintended and/or undesirable outcomes from the unavoidable mix made using gene technology. The standard of screening is ensured by regulation and containment, not molecular biology.

Even for the best understood organisms - crop plants and livestock - and least invasive techniques, that mix includes insertions of DNA from different species [39, 40].

Sovereignty

The Bill also includes provisions to erode the prerogative of New Zealanders to have a determinative say in what risks of gene technology are acceptable. Of note, exempted/non-notifiable uses include but are not limited to those listed in the Australian codes. Not only is this code developed for Australia and its context, it also can change without the consent of New Zealanders. The provision to tie our social contract to the decisions Australia makes should be removed from the Bill.

Presently the Australian exemptions include the use of genome editing to, among other kinds of activities, introduce “breaks” in DNA molecules (i.e. SDN1). New Zealand regulations may go beyond Australia’s and include SDN2 activities (allowing an exogenous DNA molecule to bias repair of the break). In our view, SDN2 and oligonucleotide directed mutagenesis have far more similarities and risk trajectories with SDN3 than with SDN1.

If adopted, this Bill would create an innovation environment in which a wide range of species with no or little history of conventional breeding experience and no history of safe use in chosen environments or in the waste stream, can be modified and released at scale by people with inadequate technical expertise in risk assessment, little or no training in genetic engineering, acting without effective accountability for either failed experiments that live and spread or the suffering that may be caused to animals in failed experiments conducted outside of constraints of institutional ethics committees.

No other country in the world to date has for this combination of proposed species breath (microorganisms, plants, animals) and process exemptions (e.g., Australia does not include SDN2) opted to remove a confirmation step, or some form of legal accountability, prior to release. By trading the country’s geographical and environmental advantages for only promises and hypothetical benefits [76, 77], it betrays an island nation that fiercely defends its natural biodiversity.

Safe products are developed in containment and verified prior to release

Promises and hypotheticals don’t need this degree of effective deregulation to prove themselves before automatic release into the environment. Real climate change resistant organisms and strategies to preserve our special, often unique, biodiversity, are not easy to

make, irrespective of legislation. However, decreased oversight will make it much much easier to make future biological pollutants through sloppy processes.

We do not concede that the status quo is fundamentally flawed; there has been no real analysis of the actual unique costs of current regulations and real evidence that they impede innovation. Whether or not it is accepted that the status quo has a determinative effect on innovation, some innovation for an unjustified imaginary of safe use is a poor trade. Legislative reform with the objective of regulation proportional to risk and in which the benefits of safe gene technology can be made more available, should be based on science.

We would welcome proposed alternatives to the status quo that streamline compliance for work done in certified containment facilities. Continued use of containment for research and development prior to intentional release would address over-reliance on experience with a limited number of species, particularly crop plants [33]. The standards for physical and behaviour infrastructure could be improved in the process. Institutions with certified containment facilities should be given strong incentives to ensure proper functioning.

Standard procedures for verifying that products of gene technology meet exemption criteria for release could be developed. Those procedures should be technology-leading rather than seen as perfunctory, cookbook, or burdens. For example, a full discussion of the NASEM recommendation that omics procedures be routinely adopted for this purpose is needed [14]. The standards of product verification should be able adapt as technology improves [36], and provide assurance to those in, visiting, or buying goods from New Zealand, that their best interests have not been compromised.

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Appendix 1 International overview of regulations
(Reproduced from Ref [78].)

Table 3: Summary of international approaches to NBT regulation

Highlighted in light green – New approaches since the release of the 1st CFS in 2021;

Grey italics – Proposed approaches, not yet in force.

	Some NBTs excluded from GMO regulation/pre-market assessment?	Criteria for exclusion	Notification/ Confirmation Required?	Year approach adopted/updated	Applies to
North America					
US	Yes	Specific criteria (refer to Table 2)	In some cases	Revised Biotechnology Regulations finalised 2020; updates ongoing	Plants and Animals
Canada	Yes[41]	Absence of foreign DNA in final plant product; no new or increase in toxins, allergens, and antinutrients; no compositional changes; no new food use	Voluntary	Updated guidance published July 2022	Plants
Europe and Middle East					
European Union (proposed)	*Yes*	*Specified maximum number of genetic modifications compared to parent plant (still under consideration)*	*Yes - proposed database*	*European Commission proposal adopted 2024, negotiations with European Council ongoing*	*Plants*
European Union (current)	No	N/A	GMO assessment framework applies	2018 decision of the Court of Justice of the European Union (CJEU)	Plants
UK (England only)	Yes	Could have been produced by traditional breeding	Yes	Genetic Technology (Precision Breeding) Act passed in 2023	Plants and vertebrate animals
Israel	Yes	Absence of foreign DNA	Yes *	2017	Plants
South and Central America					
Argentina	Yes	Absence of new combination of genetic material in NBT organism/final product free of transgenes	Yes *	2015	Plants, Animals, Microorganisms
Brazil	Yes	Absence of recombinant DNA/RNA in final organism	Yes *	2018	Plants, Animals, Microorganisms
Paraguay	Yes	Absence of new combination of genetic material in NBT organism/final product free of transgenes; prior approval in other countries with established regulatory processes	Yes *	2019	Plants, Animals, Microorganisms
Columbia	Yes	Absence of foreign DNA sequences in final organism	Yes *	2018	Plants, Animals, Microorganisms
Chile	Yes	Absence of new combination of genetic material in NBT organism	Yes *	2017	Plants, Animals, Microorganisms
Ecuador	Yes	Absence of recombinant/foreign DNA in final organism	Yes *	2019	Plants, Animals, Microorganisms
Guatemala	Yes	Absence of new combination of genetic material in NBT organism	Yes *	2019	Plants, Animals, Microorganisms
Honduras	Yes	Absence of new combination of genetic material in NBT organism	Yes *	2019	Plants, Animals, Microorganisms
Costa Rica	Yes	Absence of new combination of genetic material in NBT organism	Yes	2023	Plants, Animals, Microorganisms
Asia-Pacific					
Japan	Yes	Absence of foreign DNA	Yes *	Approach adopted in 2019, updated 2020	Plants, Animals, Microorganisms
China	Unclear how rules will apply	NBTs classified into risk categories	Yes *	Rules issued in 2023	Plants

[41] Exclusion from regulation as "novel foods", not GMOs

	Some NBTs excluded from GMO regulation/pre-market assessment?	Criteria for exclusion	Notification/ Confirmation Required?	Year approach adopted/updated	Applies to
Republic of Korea	*Proposed exemption from risk assessment*	*Absence of foreign DNA*	*Yes **	*Draft revision to regulations under consideration*	*Plants*
India	Yes	Absence of foreign DNA	Yes *	2022	Plants
Philippines	Yes	Absence of a new combination of genetic material	Yes *	2022	Plants
Singapore	*Proposed exemption from pre-market assessment*	*Absence of foreign DNA*	*Yes **	*Consultation on proposed framework completed in 2024*	*Plants*
Africa					
Nigeria	Yes	Absence of a new combination of genetic material in final product	Yes *	2021	Plants, Animals, Microorganisms
Kenya	Yes	Absence of foreign DNA	Yes *	2022	Plants, Animals, Microorganisms
Malawi	Yes	Absence of novel combination of DNA	Yes *	2022	Plants, Animals, Microorganisms
Ghana	Yes	Absence of foreign genes in final product	Yes *	2023	Plants, Animals, Microorganisms
South Africa	No	N/A	GMO assessment framework applies	2021	Plants, Animals, Microorganisms

* Exclusion is on a case-by-case basis

Appendix 2 Mutagens

(Reproduced from Ref [19].)

Table 1. Examples of commonly used physical and chemical mutagens, their characteristics, and hazard impacts.

Types	Mutagens	Characteristics (Sources and Description)	Hazards	References
Physical Mutagens	X-rays	Electromagnetic radiation; penetrates tissues from just a few millimeters to many centimeters.	Dangerous, penetrating	[59]
	Gamma rays	60Co (Cobalt-60) and 137Cs (Caesium-137); electric magnet radiation generated with radiation isotope and nuclear reactors.	Dangerous, penetrating	[59,60]
	Neutron	235U; there are fast, slow, thermal types; formed in nuclear reactors; unloaded particles; penetrate tissues up to large numbers centimeter;	Very dangerous	[59,60]
	Beta particles	32P and 14C; reduced particle accelerators or radioisotopes; electrons; ionizing and penetrating tissues shallowly	Maybe dangerous	[60]
	Alpha particles	Sources originating from radiological isotopes; helium nucleus able to penetrate tissues heavily	Very dangerous	[59]
	Proton	Present in nuclear reactors and accelerators; derived from the nucleus of hydrogen; penetrate tissues up to several inches.	Very dangerous	[59,60]
	Ion beam	Positively charged ions are accelerated at a high speed and used to irradiate living materials, including plant seeds and tissue culture.	Dangerous	[60]
Chemical Mutagens	Alkylating agents	The alkylated base can then degrade with bases to create a primary site which is mutagenic or recombinogenic or mispairs in DNA replication mutations, depending on the atom concerned.	Dangerous	[59]
	Azide	Just like alkylating agents.	Dangerous	[59]
	Hydroxylamine	Just like alkylating agents.	Dangerous	[56,59]
	Nitrous acid	Acts through deamination, replacing cytosine with uracil, which can pair with adenine and thus result in transitions via subsequent replication cycles.	Very Hazard	[56]
	Acridines	Interspersing between the DNA bases, thus distorting the DNA double helix and the DNA polymerase, recognizes the new basis for this expanded (intercalated) molecule and inserts a frameshift in front of it.	Dangerous	[56]
	Base analog	Comprises the transformations (purine to purine and pyrimidine to pyrimidine) into DNA in place of the regular bases during DNA replication and tautomerizing (existent in two forms, which interconvert into one another such that guanine may be present in keto and enol forms).	Some may be dangerous	[56]