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Submission on the Ministry for the Environment's consultation document: *Improving our GMO regulations for laboratory and biomedical research: Consultation document*.

This submission is from the Centre for Integrated Research in Biosafety at the University of Canterbury. The research centre has approximately 20 years of research experience in the topic 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 served the High Court as an expert witness in its 2014 decision *Sustainability Council Trust v. EPA*, the Auckland Unitary Plan and Whangarei and Far North District Plans, Royal Commission on Genetic Modification, and other committees. On the international level, on this topic the same author served on 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.

Authors[1]

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[1] Prepared in accordance with the Critic and Conscience of Society and Academic Freedom Policy (2018). This may not be the opinion of the University of Canterbury.

Summary

The Centre for Integrated Research in Biosafety believes that the process being followed by the Ministry for the Environment cannot be reasonably seen to be independent of the wishes of a narrow sector voice. The options presented therefore describe a spectrum of choices that are not centred as they would be in an open consultation respectful of the many sources of relevant knowledge from a pluralistic society, but skewed toward the preferences of a privileged technological/entrepreneurial elite. Therefore, if recommendations on these proposals are contemplated to be used to inform a regulation or legislation response, there should be at least one more, but proper, consultation based on concrete wording suggestions.

There should have been a consultation on options for tiering (or other frameworks) preceding this consultation which was on whether or not variations of a particular tiering approach are acceptable.

Responding specifically to the Proposals presented, we recommend that the Ministry:

- Develop for consultation draft definitions of work that can be scoped as biomedical research. The scoping should account for all types of organisms that might be modified in biomedical research, including microorganisms and tissue culture cells.
- Make explicit in each Proposal how the Minister's expectation that the proposed reforms will be limited to *the regulations and controls for GMOs used in laboratory settings and for biomedical research and development* is met and enforced.

Of the tiered-risk options presented, our view is that a modification of Option 2 described on page 21 in the Interim Regulatory Impact Statement (Kenward, 2023) has the potential to retain proportional regulatory requirements while providing the target community with the relief they desire. Option 1, especially with the inclusion of Proposal 7, in our view is a fundamental change to the objectives and purpose of the Hazardous Substances and New Organisms Act.

Notwithstanding our concern that the starting point of this consultation marginalises the interests of other stakeholders, we recommend the following additional changes:

- Proposal 7 should be deleted. If it is not, then extensive additional exclusion criteria are necessary.
- Adopt a concept of risk that is not limited to pathogenicity and then consider whether research and development leading to the creation of new organisms is in all ways of low risk to humans and the environment outside of a containment facility.
- Biosafety Committees require formal review and accountability for decisions. A legal framework similar to the PCBU concept of the Health and Safety Act (2015) should apply to institutions with biosafety committees which can determine for themselves appropriate operational practices (e.g., as pertains to but not only fermentation).
- Expand Proposal 6 restrictions to "human *and animal* embryonic stem cells, germ cells, oocytes, zygotes or early embryos." Do not exempt plant and fungi cells because their somatic cells are easily converted to the equivalent of germ cells or zygotes.

Kenward, S. (2023). *Interim Regulatory Impact Statement: Improving Our Gmo Regulations for Laboratory and Biomedical Research*. https://environment.govt.nz/assets/publications/Interim-RIS-Improving-our-GMO-regulations-for-laboratory-and-biomedical-research.pdf

Objectives

Legislation and regulations that

• _proportionately manages the risks that laboratory research poses to the environment, and to the health and safety of people and communities

• _contributes to better health outcomes for New Zealanders through better biomedical research outcomes and innovation, and through greater access to therapies and medicines

• _is not only up to date but also future-proof, to anticipate and flexibly accommodate future technological developments to the best extent possible

Response 1: **Yes**.
Response 2: We recommend a Responsible Research and Innovation approach to achieve the objectives (Agapito-Tenfen et al., 2018; Foley et al., 2016; Roberts et al., 2020). This could be aided by adoption of a mix of reflexive analytical tools (Saltelli et al., 2020). We suggest a framework based on the properties inherent in technology and not ambiguous terminology. A possible alternative framework is tiering according to critical control points (Heinemann et al., 2021) rather than the semantics-based tiers suggested in Proposal 1.

The Minister said: "*At its simplest, biotechnology is technology based on biology."* This banal observation fails to define biotechnology. It provides no insight into why and how biotechnology should be regulated any more than it would be to say that nuclear weapons are technology based on physics and airplanes are technology based on aerodynamics.

Technology is the term with which to start (Figure 1). Our definition is "a way that people speed up or concentrate natural phenomena" (Heinemann, 2022). Technology based on biology is a set of techniques with three shared characteristics (Heinemann et al., 2023). 1) It allows people to cause more harm faster, even if it also creates benefits. 2) The potential for harm increases with more use of the technology, but safety does not. 3) Regulations can control harm scaling.

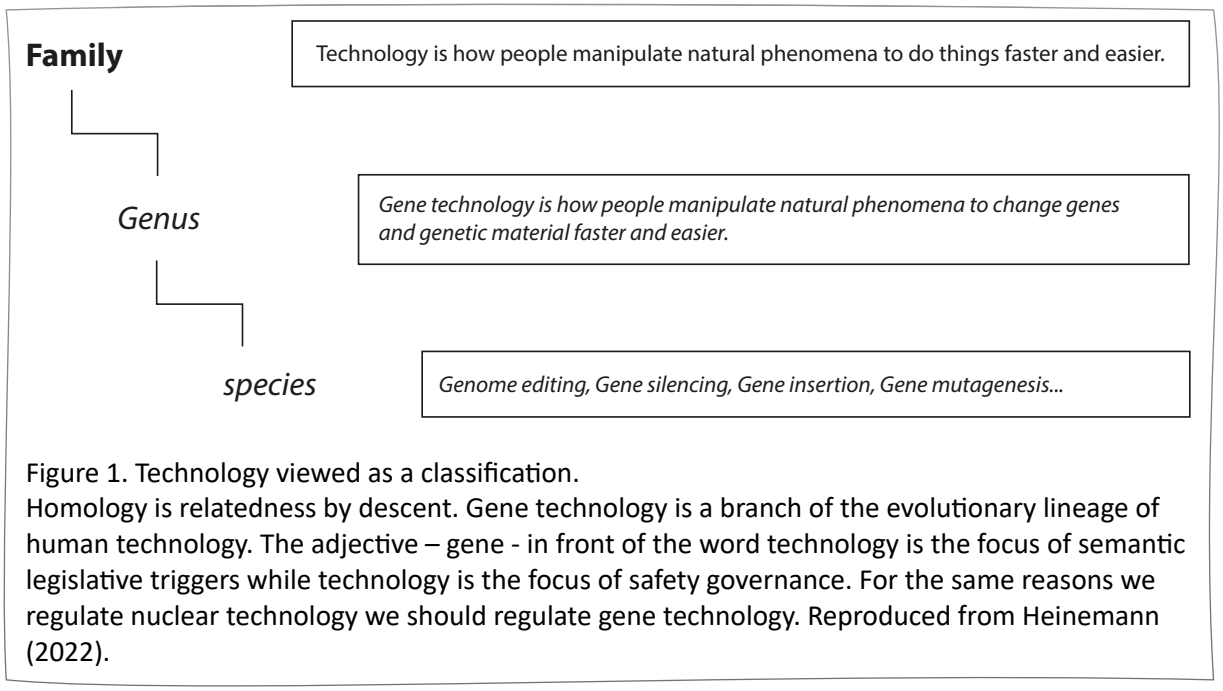

Figure 1. Technology viewed as a classification.
Homology is relatedness by descent. Gene technology is a branch of the evolutionary lineage of human technology. The adjective – gene - in front of the word technology is the focus of semantic legislative triggers while technology is the focus of safety governance. For the same reasons we regulate nuclear technology we should regulate gene technology. Reproduced from Heinemann (2022).

"Techniques of gene technology can be grouped, like members of a species, by shared characteristics. The distinguishing feature is harm scaling rather than similarity of hazards created through technological or natural processes" (Heinemann et al., 2023).

Scaling is "the property that makes it possible to deliver the benefits [a technology] promises at commercial time and production scales. The source of inseparable potential for harm is this same property that creates hazards at scale. Scale-triggered regulation of gene technology unifies the management of various methodologies under a common risk genus, or technological trajectory. It provides consistency and clarity to regulations" (Heinemann et al., 2023). Importantly, this approach significantly reduces the need to litigate over word puzzles or to create new undefined terms to try and clarify older ambiguous terms (see discussion on Proposal 7, below).

Without a shared and meaningful understanding of what biotechnology is, policy becomes a jumble of interests, compromises, and frustrations. Potentially significant long-term costs are transferred to society. We should at least agree that a definition of biotechnology as technology based on biology is not a solid foundation.

The consultation document reads as a response to the concerns and opinions of a privileged voice.[2] An example of how close the Ministry is to the privileged voice is the Minister's statement that "*At its simplest, biotechnology is technology based on biology.*" The sentence is directly lifted without attribution from a biotechnology industry website (Figure 2). Those privileged voices, only a slice of society, not only define the problems for the Ministry to solve, but they provide the Ministry with a veil of confident reassurance that their conception of risk is settled science, even settled beyond the science. It isn't (NASEM, 2016).

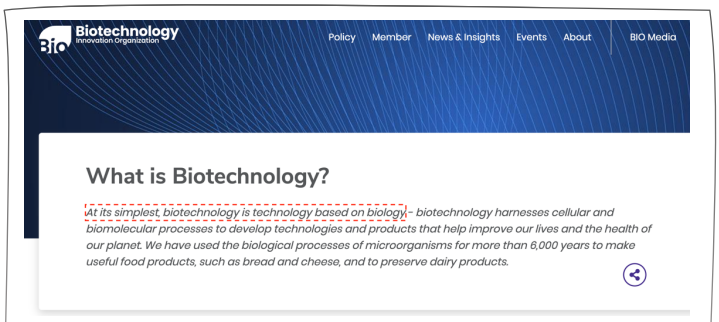

Figure 2. Screenshot (17.07.23) of Biotechnology Innovation Organization (formerly Biotechnology Industry Organization) website. BIO describes itself as "the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations."

[2] This is conceded in the *Interim Regulatory Impact Statement: Improving our GMO regulations for laboratory and biomedical research* which says "One limitation of the analysis for this policy work is that the evidence base used to support the need for policy changes and to establish issues/issue areas consists primarily of the viewpoints of researchers, organisations, companies, and government agencies" Kenward, S. (2023). *Interim Regulatory Impact Statement: Improving Our Gmo Regulations for Laboratory and Biomedical Research*. https://environment.govt.nz/assets/publications/Interim-RIS-Improving-our-GMO-regulations-for-laboratory-and-biomedical-research.pdf. The Statement then attempts to minimize this limitation by saying that the privileged voices "have a high level of relevant expertise and are respected in this area. These individuals and groups include the Office of the Prime Minister's Chief Science Advisor, Crown Research Institutes (CRIs), professors and lead researchers at New Zealand's largest universities, the Royal Society Te Apārangi, and the Productivity Commission" ibid.. Yet this source of expertise is also a source of conflict-of-interest which is not evaluated by the Ministry. Neither does it present an analysis of the processes undertaken by the listed organisations and how well they may or may not have balanced the selection process of participants informing their views. An implication of the Ministry's evaluation is that there would be no compelling contrary views from people and groups that were also respectable.

The recurrent theme from the biotechnology research and development (including academic) community is a fear of external regulation. Yet there is no evidence that external regulation has failed to deliver safe products.

> *"External regulation has been a stone in the biotechnologists' shoe since the very beginning of genetic engineering. Most genetic engineers believe that their field has successfully self-policed ever since the 1975 Asilomar conference, when scientists convened to discuss safety issues and established a moratorium on certain hazardous experiments. From this regulatory origin myth has grown a widespread conviction that external regulation has been excessive and misguided, with anti-GMO alarmists to blame. Frustration on this point has fueled scorn for imposed precautions, scorn that is already transferring to the CRISPR debate"* (Stone, 2017).

There is more to the technology than negligible, low, medium, and high risk in a unidimensional conception of biological harm (NASEM, 2016). The technology is not static, any more than are the various environments and mixtures of its products. No one can forecast risk with the kind of precision being relied upon in the consultation document. The process behind this consultation document resembles "*a 'reductive aggregative' theoretical framework based on subjective expected utility. This seriously foreshortens the real depth and breadth of stated challenges around* 'uncertainty and risk-taking'" (Stirling, 2023).[3]

We hope that upon reflection of our submission, the Ministry would ask itself again was "the framing of the problem incomplete? Does the framing include its political (as opposed to technical) dimensions, or was the technique, and its numbers, used to obfuscate and distract?" (Saltelli et al., 2020).

The consultation document does not describe commensurate effort to understand the uncertainties and asymmetry of risk-taking. Neither does it convincingly demonstrate that benefits will be significant or achievable. We suggest that this is a symptom of the *immaturity of the conversation* on gene technology in Aotearoa New Zealand and contributes to the problem of achieving a sustainable social license.

Efforts to future-proof the regulations appear to default to a technological imaginary where uses of gene technology all become in some (narrow) sense safer. Consideration of the potential for emerging techniques and products to create risks when used at larger scales, risks that cannot be anticipated at present, is nonexistent. This is what Stirling calls a "theoretical framework based on subjective expected utility" (Stirling, 2023). The US National Academies of Science cautioned against this in their 2016 report (NASEM, 2016). That report was on GM crops, but their advice generalises to the organisms in the consultation document.

The Academies do not project a future where safety is an obvious outcome of using the "new techniques" that become available. Instead, they call for new approaches to ensure that the techniques are used to create safe products.

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[3] The confusion manifests clearly in how the Ministry compares existing practice of gene technology, which has benefitted from a legislated risk assessment process, to a hypothetical low risk potential of some applications of gene technology outside of future regulatory oversight. In the *Interim Regulatory Impact Statement: Improving our GMO regulations for laboratory and biomedical research* it restates the EC observation that in essence 25 years and 500 *plant biotechnology* researchers think that GM crops "are not *per se* more risky than e.g. conventional plant breeding technologies" ibid.. The Ministry is proposing to remove the one critical step that requires that equivalence for risk to be established, and has provided regulatory power to ensure it. We emphatically note that equivalence of risk is not something that can be extrapolated from equivalence between two arbitrarily chosen comparators but extends to how quickly a harmful product can be manufactured by accident or oversight. This framework is embedded in the regulation of many technologies, from aircraft manufacture to nuclear power. There is no clear rationale for it not being applied to gene technology.

> *"There is an urgent need for publicly funded research on novel molecular approaches for testing future products of genetic engineering so that accurate testing methods will be available when the new products are ready for commercialization"* (NASEM, 2016).

Furthermore, they advocate mechanisms through which regulators can retain a watch on the modified organisms rather than create exemptions from risk assessment (e.g. Proposal 7).

> *"Regulatory agencies responsible for environmental risk should have the authority to impose continuing requirements and require environmental monitoring for unexpected effects…"* (NASEM, 2016).

Like us, the US National Academies recognised the risk of a narrow approach to regulation of gene technology. The risk is not in the similarities of organisms produced using them with those isolated through observation (conventional breeding), but in the many ways they can be different biologically, socially, and at scale.

> *"Not having government regulation of GE crops would be problematic for safety, trade, and other reasons and would erode public trust"* (NASEM, 2016).

[Most references are open source.]

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Proposal 7: Clarify the regulatory status of certain biotechnologies

We begin with Proposal 7 because it has overarching implications for the consultation.

The Ministry's perceived benefits:

• provide greater clarity and certainty to researchers, organisations and biotechnology companies, potentially encouraging increased use of these biotechnologies in research and in the development of biomedical therapies

• codify previous statutory determinations that researchers may not know of or be able to readily discover

can adequately be achieved without Proposal 7. We are neither convinced that the present set of definitions and the existing non-GMO Regulations are causing significant costs or problems of access to biomedical therapies, nor that any benefits from this Proposal would be significant measured against research and development timelines. [4] The potential trade-off is that this Proposal undermines the objectives and purpose of the Act.

According to the Minister: *"This consultation is about the regulations and controls for GMOs used in laboratory settings and for biomedical research and development. We are not looking to change the rules related to field trials and releases of GMOs into the environment."*

Adopting Proposal 7 would make the Minister's words a fiction. The Ministry has admitted this point but not addressed it in the consultation document. In the Interim Regulatory Impact Statement it says that "while amending the definition of a 'genetically modified organism' to deregulate certain types of research (or certain types of genetic modification techniques) would lower the regulatory requirements for that research, it would also mean that conducting that research in the environment would not be prohibited" (Kenward, 2023).

The changes to the non-GMO definitions in Proposal 7 deregulate some GMOs and allow their unsupervised release from - or even their manufacture outside of - containment. Proposal 7 is therefore not an exemption from the Regulations (and about streamlining laboratory settings), but effectively an exclusion of some GMOs and processes from the scope of the Act.

Furthermore, the Ministry has a mono-dimensional and pre-determined view of risk, defining it only in terms of the pathogenicity of organisms, as in "This review is also focussed on low-risk research (ie, not involving pathogenic organisms), and unless specified, changes to the provisions for higher-risk organisms are not within scope. That is researchers surveyed by MfE specifically highlighted the disproportionate stringent regulations for very-low-risk and low-risk GMOs, but no issues were highlighted with the regulations for higher-risk research" (Kenward, 2023). ***Risk of harm from new organisms to human health or the environment is not just from pathogenicity, and certainly not just from pathogens of people.***[5]

[4] The lack of evidence is acknowledged in the *Interim Regulatory Impact Statement: Improving our GMO regulations for laboratory and biomedical research* which says: "While the absence of evidence that the HSNO Act is holding back research and biomedical therapies may point to there being no problem with the regulatory settings" ibid.. The Ministry then invokes a hypothetical and invisible impact saying: "it may also be the case that the regulatory settings are holding back research and biomedical therapies but not in a way that would provide tangible evidence" ibid.. We find it difficult to imagine significant impacts that evade any form of measurement.

[5] This is an example of conflating risk and tools of biological containment, the use of 'low risk microorgansisms'. Organisms with low risk of being pathogens are unlikely to cause an infection in laboratory workers or the community if they escape containment, but they are not in all circumstances necessarily harmless to the people or the environment.

We emphatically recommend instead that the proposed processes only be exempted from some GMO regulations as they apply in a laboratory setting and only while the organisms remain secure in a containment facility.

We do not agree with the proposed transfer of organisms that fit the proposed definitions to the non-GMO list.

Response 24: **No**. We do not agree with this framing and neither do we support the proposed change to the non-GMO regulations.[6]
Response 25: **Yes**. We list these below and caution that we feel that even adopting improved criteria would still be an outcome far inferior to withdrawing Proposal 7.
Response 26: **No**. We do not agree with the issues outlined. Their framing is factual information presented in a misleading way.
Response 27: **Yes**. There are better frameworks for achieving regulatory clarity and proportionality to regulation. Examples are provided in this submission. They would also resolve any uncertainties about other 'biotechnologies'.

While the Ministry is seeking to provide regulatory clarity and certainty for the research and development communities by way of Proposal 7, it only achieves a shift from ambiguous and contested terms to other ambiguous and contested terms. It creates the appearance of resolving conflict but transfers the conflict to terminology that will precipitate future debate and not result in superior regulatory clarity.

In some cases Proposal 7 reduces ambiguity by narrowing genetic and biochemical concepts. It does not improve clarity for risk assessment. This might suit some scientists and regulators, but it is not representative of how these words and concepts are used in genetic science as a whole. It focuses regulators' attention to sources of hazards rather than keeping focus on risk, undermining the objectives and purpose of the HSNO Act.

Through Proposal 7 the Ministry introduces new terminology (eg "genetic makeup", "genome") and associated definitions, substituting narrower terms than used in the HSNO Act (e.g., substituting "DNA" for "nucleic acids").

Genetic makeup is described as "the modification of the DNA in their genome". The HSNO Act does not define a genome and there is not a generally consistent understanding of the genome *in the context of risk assessment*, much less that it is only a composite of DNA (Fitz-James & Cavalli, 2022; Miska & Ferguson-Smith, 2016; Shah et al., 2021).

The references we provide above demonstrate that for the international risk assessment community exclusion of all epigenetic modifications from GMO regulations is taking scientific liberties and is not just a clarification of terms. Closer to home, we note that the s26 determination 30 June 2021 on application APP203395 excluded particular epigenetic modifications arising in the context of an "siRNA response" (which is also limited to eukaryotes). Other than epigenetic modifications of the type that occur as an siRNA response in eukaryotes, to our knowledge no other kinds of epigenetic modifications in any other kinds of cells have been determined to be out of scope of the existing legislation.

[6] We could be amenable to an exemption from some regulations for work that involved the processes described in Proposal 7 (the introduction of RNA, the introduction of DNA, epigenetic modifications) along with revised exclusionary criteria, provided that the work was still conducted in a compliant containment facility. We do not support exemption from the GMO regulations for organisms that would then transfer to a contained field trial or be released.

The Proposal goes well beyond the scientific and legislative framework in New Zealand and abroad by inclusion of any and all, even yet to be discovered - *in fact not defined* - epigenetic modifications.

Moreover, the Proposal is not consistent with existing wording from the HSNO Act. The Act describes a GMO as "any organism in which any of the genes or other genetic material" have been modified. Genetic material means material that is relevant to the heritable traits of an organism. *The Act expresses no preconceptions about its chemical composition*. Proposal 7 would limit the scope of the legislation by narrowing a concept that Parliament left open.

Furthermore, the Act establishes a link between genes and other genetic material and genetic elements (of new organisms) which it does define. In doing so Parliament has broadened the definition of genes (of which a genome is comprised) and this serves the Act's objectives to protect human health and the environment.

Genetic element means: "(a) *heritable material; and (b) any genes, nucleic acids, or other molecules from the organism that can, without human intervention, replicate in a biological system and transfer a character or trait to another organism or to subsequent generations of the organism."* The Act (sections 44(A)(2)(c) and 45(A)(2)(b)) specifically references genetic elements with respect to the mitigation of risk from the development or testing of genetically modified organisms outside of a containment facility. If risk can be transmitted either infectiously or through reproduction, the cause is a *gene, nucleic acids, or other molecules* that may be composed of material "that can, without human intervention, replicate in a biological system…" (HSNO Act section 2).

We suggest that Proposal 7 would achieve "clarity" by undermining the scope, and consequently the purpose, of the Act. The purpose of the Act is "to protect the environment, and the health and safety of people and communities, by preventing or managing the adverse effects of hazardous substances and new organisms" regardless of the structure of the molecules within these organisms through which that risk is transmitted, or what they are called (i.e., genes vs epigenes). Arbitrarily narrow and contestable definitions of triggers, such as DNA or genes, undermines the objectives and purpose of the Act. (This is a key observation and applies to our response to Proposal 1.)

> *"[T]he advocated methods tend to treat multiple ambiguous, complex, contested, qualitative dimensions as if they can be satisfactorily reduced to a few, ostensibly precise, scalar numbers. The resulting calculations elide differences between apples and oranges; blinker attention to focus disproportionately on the most readily quantified aspects; diminish the significance of intractable ignorance; neglect many sources of variability and sensitivity; and so conceal the irreducibly political (rather than technical) aspects of research evaluation"* (Stirling, 2023).

Our advice is that Proposal 7 be deleted. Should Proposal 7 proceed, then additional exclusionary criteria are needed. In addition, further definitions are required to make the exclusionary criteria effective. At a minimum, the nucleic acids RNA and DNA need to be defined. The properties of these molecules with respect to hazard pathways may be fundamentally altered by small chemical modifications to the base molecule (Thaler et al., 1996). For clarity and to provide certainty to stakeholder communities, exclusionary criteria should apply to nucleic acids that have been modified.

The exclusionary criteria should not be quantitative. That is, it would be a ridiculous exercise to define how much of a molecule must be DNA or RNA for the molecule to be called DNA or RNA.[7] In addition, the criteria should not be limited to molecules modified by covalent bonds. Doing

[7] The properties of a molecule can be fundamentally reshaped by seemingly small modifications. "*The apparently small difference in backbone structure between DNA and RNA (one hydroxyl group at the 2' position of the sugar) has profound consequences*" Thaler DS, Liu S, Tombline G. 1996. Extending the chemistry that supports genetic information transfer in vivo: phosphorothioate DNA, phosphorothioate RNA, 2'-O-methyl RNA, and methylphosphonate DNA. *Proc Natl Acad Sci USA* **93**: 1352-1356.

otherwise will not future-proof the Regulations.[8] Instead, the criteria should specify what properties a molecule with nucleotides *must **not*** have to be pre-determined as exempted from creating a new organism.

Additional exclusionary criteria

Proposal	Problem	Minimum additional exclusionary criteria if proposal is not withdrawn.
The introduction of ribonucleic acid (RNA) into an organism provided that it cannot result in an alteration of the organism's genome sequence.	If a genome is described as composed only of DNA then this activity is defined as outside the scope of the legislation. *That would be an error.* The use of RNA can result in changes to DNA, and some (even eukaryotic) organisms have stable RNA elements in their genomes that could be changed by the introduction of RNA (Heinemann, 2019). Very few organisms - if any - have been described to a level that provides confidence that we know what is the complete chemical description of their genomes. In particular, the undescribed diversity of microbial and fungal species is enormous. Nevertheless, it is already known that some organisms have a mix of RNA and DNA genomes. Specifically, strains of the yeast *Saccharomyces cerevisiae* have stable RNA components in addition to their chromosomes composed of DNA. The effect of this 'clarification' would be to make it possible, without substantial social oversight or risk assessment, to use RNA-based formulations to alter traits and heritable traits in organisms outside of containment, at will, and at scale (Heinemann & Walker, 2019). The exclusion criteria adopted by the Australians is far more prescriptive and should be the minimum adopted by New Zealand. The regulatory amendment specifically constrains the dsRNA molecules used in any kind of treatment in the following ways. "This item provides that techniques involving applying RNA to an organism to temporarily induce RNA interference are not gene technology, provided that:	-RNA for applications other than human or veterinary medicine that have • benefited from a similar testing and development process and risk assessment approval process as defined in relevant legislation. • been administered by registered physicians or veterinarians who would also be accountable for keeping administration, storage and disposal records, and have a general duty to report adverse effects. [Meaning a specific delivery dose controlled by the health professional.][10] -RNA that has not been chemically modified. -RNA that does not form double-stranded secondary structures or bind to another RNA molecule to create double-stranded RNA either before or after introduction into an organism.

[8] See, for example Heinemann JA. 2019. Should dsRNA treatments applied in outdoor environments be regulated? *Environ Int* **132**: 104856, Thaler DS, Liu S, Tombline G. 1996. Extending the chemistry that supports genetic information transfer in vivo: phosphorothioate DNA, phosphorothioate RNA, 2'-O-methyl RNA, and methylphosphonate DNA. *Proc Natl Acad Sci USA* **93**: 1352-1356. From Thaler et al (1996): "Chemical variants of DNA and RNA backbones have been used in structure-function and biosynthesis studies *in vitro*, and in antisense pharmacology, where their properties of nuclease resistance and enhanced cellular uptake are important." "This study extends the chemical structure of nucleotides that are known to be competent to transfer genetic information *in vivo*."

[10] For guidelines, see http://www.nzva.org.nz/policies/9a-vaccine-use-companion-animals-new-zealand?destination=node%2F2212.

	• the RNA cannot be translated into a polypeptide • the organism's genome sequence cannot be altered as a result, and • an infectious agent cannot be produced."[9]	
The introduction of DNA into an organism provided that it cannot be independently replicative	(1) Presumably this criterion means that the DNA is not expected to have (*cis*-acting) sequences that would allow amplification or maintenance by polymerases already in the cell. The resulting organisms are what many refer to as null/negative segregants. For a variety of good reasons, they should not be excluded from the GMO regulations because their risk level cannot be generically predetermined (Heinemann et al., 2023). (2) Not expecting a DNA molecule to replicate is far from demonstrating that it does not. DNA molecules without known replication-directing sequences in an organism can nevertheless at least sometimes be replicated and thus have the potential to be passed on, even if intermittently, to descendants (Srivastava & Ow, 2003; Stinchcomb et al., 1985). This also increases the probability of acquiring a more efficient replication. An experiment showed that the cloning plasmid pBR322, which is only known to replicate in some bacteria, could by *any* of 10 unlinked small sequence changes be converted into a plasmid that replicated very well in eukaryotic cells (Kipling & Kearsey, 1990). The authors concluded "that changes in replication origin distribution may arise de novo by point mutation." The level of replication is a matter of technological capacity to detect the products of replication. That will vary by organism and cannot be assumed knowledge for all organisms and all DNA sequences.	-DNA for applications other than human or veterinary medicine that have • benefited from a similar testing and development process and risk assessment approval process as defined in relevant legislation. • been administered by registered physicians or veterinarians who would also be accountable for keeping administration, storage and disposal records, and have a general duty to report adverse effects. [Meaning a specific delivery dose controlled by the health professional.][10] -DNA that has not been chemically modified. -DNA that cannot result in the production of a transcript that could form a double-stranded RNA molecule.
Epigenetic modification	Epigenetics is "the study of molecules and mechanisms that can perpetuate alternative gene activity states in the context of the same DNA sequence" (Fitz-James & Cavalli, 2022). It is not limited to gene expression control and epigenetic modification is not limited to only modification of gene expression, as stated in the Ministry's proposal. An epigenetic trait can be a pattern or state of expression that, once established, is stable for long periods of time in a long lived non-dividing cell/organism, heritable through cell division	-must be incapable of causing an adverse effect to the organism, environment, or human health.

[9] https://ir.canterbury.ac.nz/items/dd48fccc-7cf1-49fc-a9b3-174d7b23b1e7.

	within an organism, or transmitted to offspring by reproduction of the organism (Bošković & Rando, 2018). It can be an altered protein conformational state that is transmitted infectiously, such as a prion (Levkovich et al., 2021). Without a rigorous underlying definition and scoping of the term 'epigenetic modification', the Ministry is creating ambiguities that either undermine the objectives and purpose of the HSNO Act or the platform for future litigation. "Epi" is not what matters for risk assessment and the purpose of the HSNO Act. What matters is the stability of the trait over time in the organism and whether the number of generations through which a particular epigenetic trait may transmit (either infectiously or by descent in an organism) would prevent it from causing an adverse effect.	

[Most references are open source.]

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Proposal 1: Introduce a risk-tiering framework for laboratory research.

Response 3: **No**. Moreover, we suggest a tiering based on defined critical control points to better meet the objectives. However, if the tiering framework of Proposal 1 is retained, it should at least be modified.
Response 4: Under the Proposal, risk-tier 2 should be the first risk-tier and risk-tier 1, as presented, should be deleted. In other words, the more appropriate action is Option 2 (p. 21) of the Interim Regulatory Impact Statement.
Response 5: **Yes**. (1) Abandon this emphasis on the research and development community's wants, and privileging their choices, with the RRI framework for biotechnology governance. (2) Consider adopting risk tiering based on critical control points (Heinemann et al., 2021).

According to the Minister: *"This consultation is about the regulations and controls for GMOs used in laboratory settings and for biomedical research and development. We are not looking to change the rules related to field trials and releases of GMOs into the environment."*

Risk-tier 1 is effectively an approval for direct release to the environment and therefore not restricted only to the regulations and controls of GMOs used in laboratory settings. Furthermore, the proposed new framework has no provision to ensure that organisms conforming to this tier are developed specifically for biomedical research and development.

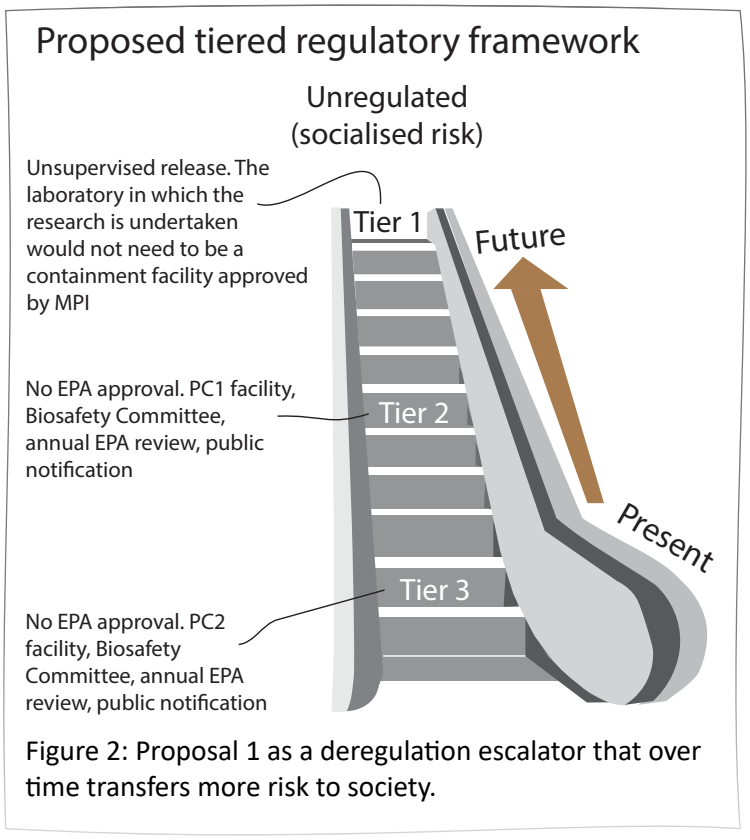

Figure 2: Proposal 1 as a deregulation escalator that over time transfers more risk to society.

Tier 1 allows development work to occur in any environment. 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.[11] Presently proposed "exempted" modifications (Proposal 7) will incentivise semantic strategies to work around the Regulations.

Developers will likely try to describe DNA modified by small molecules as DNA. They will skip around the regulations by modifying "epigenes" that could still be stable for 100s of generations, or decades in long-lived organisms. Along with

[11] 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.*"

Proposal 10,[12] all this adds up to an escalator effect that moves risk only in one direction: to the public (Figure 2).

"*[D]one properly, regulation represents the formal statutory public responsibility of a new technology, and its governance. Regulation sets bounds to what can be done, who can do it and under what conditions can things be done. But if there has been no discussion with the public, this could be argued to be a case where regulation has been socially premature, and not done on behalf of the society*" (Bruce & Bruce, 2019). The proposed "tier 1" removes bounds on who can do it, under what conditions[13], and without specific discussion with the public for some applications of gene technology, without reducing social and environmental risk.

The proposed risk-tier 1 organisms could be made into GMOs and treated as if they were listed on the non-GMO Regulations.

Moreover, it is now clear that in the near future developments in biotechnology will mechanise modification techniques to achieve greater scales and efficiencies.[14] The efficiencies are expected to be high enough that the techniques can be applied in the open environment. The techniques will allow for ***serial*** applications that can create a combination of changes that would have been regulated at a higher tier if done in one step.

The Ministry rationale for Proposal 1 is that "It is also highly likely there is research that is of such low risk that a containment facility requirement may be unnecessarily stringent. Researchers surveyed by the Ministry noted that many low-risk organisms present essentially zero risk to the environment, or to the health and safety of people and communities."

"Highly likely" is an assurance without accountability. As mentioned previously, the Ministry has applied a low threshold of conflict testing for its sources.[2] Which researchers think this? How do they know? How did the Ministry choose them? How does the full scientific community see the evidence for such grand assertions and how does the Ministry evaluate any conflicting evidence or uncertainty in the conclusions (Box 1) (Saltelli et al., 2020)?

Determining likelihood, of a good or bad activity, is the **purpose and role of a risk assessment**. Regulations describe the methodology and standards of a risk assessment. Side-stepping a risk assessment leads to risks that may not be apparent to all biotechnology users, but is to a critical risk assessor.

> *"In addition, biological actives used in technologies that allows DNA, RNA, and proteins to be delivered to cells, tissues, and organisms in the open environment may evade risk assessment and regulatory review because they are often excluded from the category of hazardous chemicals and are actively being excluded as agents of genetic modification. This emerging oversight vulnerability could lead to dual use or unintended harm to human health or the environment (Heinemann and Walker, 2019). As we cannot get an affirmative answer on the question whether all possible genetically modified foods are safe, we could not foresee what it would bring about if artificial life was released in nature"* (Li et al., 2021).

Regardless of whether some researchers think that some products can be pre-determined to be safe, not all do.[15] In any case, jumping to this outcome would be a further provocation of the tender social

[12] Proposal 10: Require regular reviews of regulatory settings

[13] With the exception of fermentation as discussed in Proposal 8.

[14] "Biologically active substances and vectors may escape risk assessment and regulatory review because they are often excluded from the hazardous chemical category and are explicitly excluded from the category of 'genetically modified agents.' This emerging oversight loophole could lead to dual-use allocations or unintended harm to human health or the environment" Li J, Zhao H, Zheng L, An W. 2021. Advances in synthetic biology and biosafety governance. *Front Bioeng Biotechnol* **9**: 598087.

[15] "Insisting on notions of 'consensus' in science for policy may imply a misrepresentation or a banalization of the opinion of dissenters, which may lead to further radicalization, while at the same time neglecting power

biotechnology contract that already exists in Aotearoa New Zealand. What is being proposed here is an example of a process that extends conflict rather than addresses it. That is why the Ministry should reconsider its methodology for seeking a renewed social license (Saltelli et al., 2020).

In practical terms, the Proposal is relying upon a hypothetical and informal risk assessment, without reference to unknown future developments (Mueller, 2019), instead of a valid and rigorous, case-by-case risk assessment. Doing the latter requires that:

- any genetic modification made (even to a restricted list of organisms) would create no new hazards;
- the risk is independent of the scale at which these modifications can be made and products released;
- the description of the ecological systems into which they could be released is irrelevant (a condition that axiomatically may be impossible to meet); and
- the standard at which these questions have been answered is valid.

Overall, the Proposal makes an unconvincing case that adoption would make a difference to medical research, much less revolutionise it. Research in other countries on the impact of similar regulations on medical research have not found that they have a significant effect above and beyond what is normally required for that kind of research (Corneliussen, 2005). **Personnel safety and laboratory contamination requirements and documentation for research or commercial reasons will ensure that the administration burdens remain, but will be relaxed only for outcomes that might cause adverse effects outside of the laboratory.**

The Ministry also concedes this very point in Proposal 6 by saying "In addition, stringent measures taken by researchers to eliminate environmental contamination to these cells means their inadvertent escape from their containers is also highly unlikely." The case is not made that the Regulations as they are now, or modestly modified as per Proposals 4-6, 8 (with qualifications), are disproportionate or costly burdens.

In an alternative critical control points framework, however, many of the same proposed advantages could be achieved without creating the obvious, and in our view irresponsible, social and environmental exposures. The ccp approach is not a procedural revolution but instead a way to make the framework consistent and clear for the research and development sector. The present use of contestable terminology and use of invalid comparators (e.g. mutations like mutations that occur in nature) as gates between different regulatory requirements leads to frustration and low quality policy.

The ccp approach can be adopted without any narrowing of legislative scope. In fact, there is an advantage to the historic practice to define gene technology (or new organism) broadly. Rather than regulate by exclusion, which is the essence of the risk-tier system and definitional changes described in the proposal, regulation is focused on the risk transitions. Risk-tiering has a focus on the characteristics of the organism. However, those characteristics do not describe an inherent but instead a conditional hazard. A ccp approach eliminates or mitigates risk where there is a hazard rather than a putative hazard wherever it is.

Hazard may not be an inherent feature of an individual, such as pathogenicity, but a feature of the process, as in the unpredictable variety of products that could be made in a short time, or released

games and relationships when high interests are at stake" Saltelli, A., Benini, L., Funtowicz, S., Giampietro, M., Kaiser, M., Reinert, E., & van der Sluijs, J. P. (2020). The Technique Is Never Neutral. How Methodological Choices Condition the Generation of Narratives for Sustainability. *Environ Sci Policy*, *106*, 87-98. https://doi.org/https://doi.org/10.1016/j.envsci.2020.01.008

at a high concentration all at once. Such circumstances are extraordinarily rare or non-existent in nature, but are the expected outcome of technology.[16]

In Figure 3 we illustrate how the special case of medical research and development could be streamlined with appropriate controls to achieve the objectives. It also does not mislead society into the impression that the changes would have no effect on requirements for release because it does not change the requirements for release.

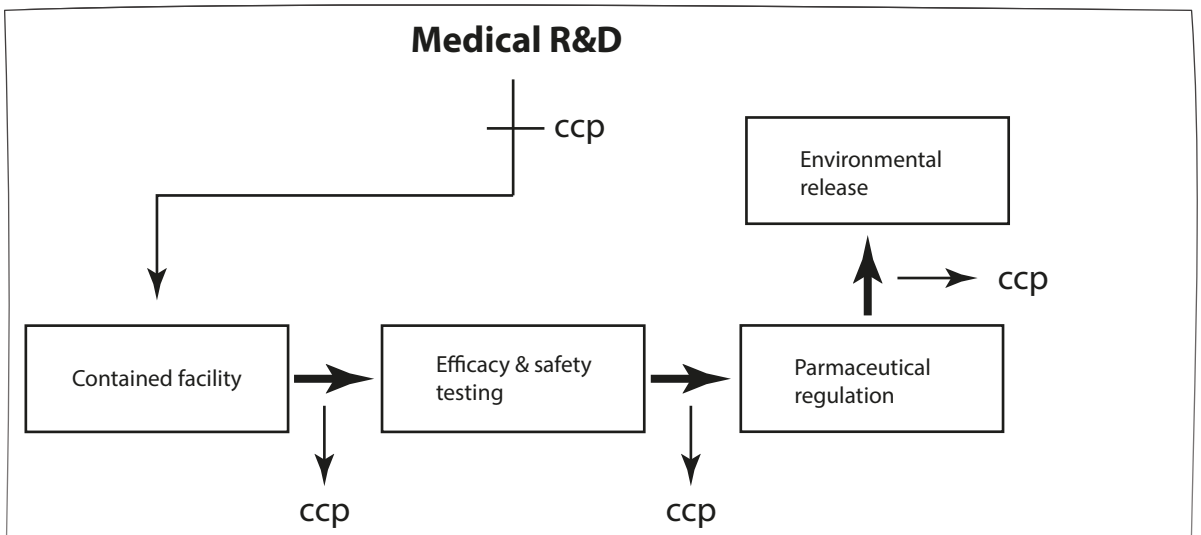

Figure 3. A critical control points (ccp) approach to streamlined Regulations. (from top) The first ccp is a gate determining whether the research involves GMOs as per the HSNO Act and is specific to human or veterinary medicine. Passage through this gate is automatic to a containment facility (possibly as relaxed as that described by the proposed risk-tier 2). The particular containment facility is a matter of assessment by the proper authority (e.g. a Biosafety Committee or EPA). The next ccp is a gate through which any GMO must pass to exit a containment facility (note, this is not the same as transfer between equivalent facilities). Passage through the next gate occurs when approval to use the product as a human or veterinary medicine under supervision is granted. In the case of medicine R&D, additional regulations apply because they are imposed by other legislation. These are expected to control most hazards independently of HSNO Act Regulations, but could be reviewed to ensure that they do. Only for the equivalent "Dealings involving intentional release" would unsupervised release require a final evaluation at the ccp from supervised use in patients to unsupervised use in the environment. These are consistent with present Proposal 2: Reduce the assessment and approval for medicines that are, or contain, new organisms, but do not extend to present Proposal 1 risk-tier 1 inclusions.

In Figure 4, we illustrate how the use of gene technology for any other research or development purpose would be streamlined. From the perspective of researchers or clinicians, HSNO Act compliance is reduced.

[16] Note that the ccp approach could be applied to all biotechnology, not just gene technology.

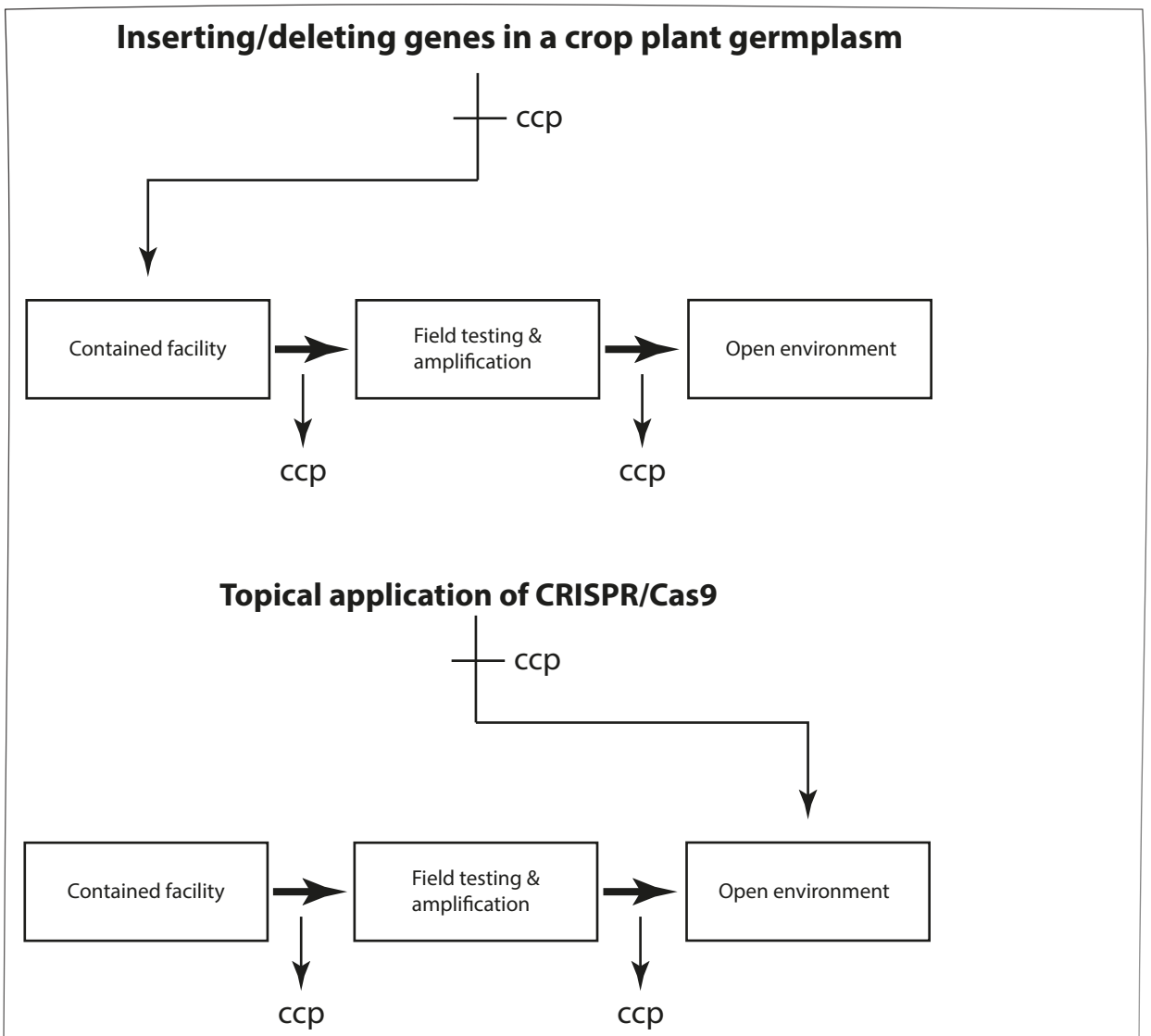

Figure 4. A critical control points (ccp) approach to streamlined Regulations for present and near future applications of genome editing. (top) When developing a new crop plant the first ccp is a choice to use gene technology. If yes, then the work advances to a containment facility (with specifications possibly as relaxed as described for risk-tier 2 in the present proposal). A decision to move the work outside of a contained facility, or beyond a field trial, is an activity with a new potential scale for hazard and defines the next ccp. The contained facility that is needed for biosafety is identical to the facility used at present to make the intended modifications. Biosafety is also assured. However, it is not true that the containment facility must run at these standards exclusively for biosafety reasons (Heinemann et al., 2021). (bottom) The hypothetical but near future case of direct application of gene technology in the environment. Here there exists only one ccp, between choice to use a gene technology and release into the environment. As per the Minister's statement that the suggested changes to the Regulations will not alter what may be released into the environment, this ccp should not escape full consultation and risk assessment.

The logic of the risk assessment is consistent when it is focused on activity changes that cause a change in the potential for an adverse effect (Heinemann et al., 2021). Those changes are critical control points rather than formulistic and assumption-burdened descriptions of particular molecules such as DNA or genome or similes between technology and nature (for further elaboration, please see our response to Proposal 7, above).

Box 1: Risk assessment is not a measure of uncertainty in measurement.

A common policy error is to equate risk with uncertainty (Stirling, 2023). A risk assessment is a normative judgement that arises from a composite of evidence that may be quantitative or qualitative, highly precisely measured or shot from the hip.

Privileging simple authority statements made by those from a technical community is a symptom of the problem:

> *"It is also highly likely there is research that is of such low risk that a containment facility requirement may be unnecessarily stringent. Researchers surveyed by the Ministry noted that many low-risk organisms present essentially zero risk to the environment, or to the health and safety of people and communities."* Source: MfE consultation document

Even as members of the same technical community, it would be beyond us to know upon what evidence the Ministry's informants rely. It may come from a belief dating back to the late 1970s in the inviolability of biological containment. "*From its inception, it represented a confidence and presumption that living entities could be engineered to contain themselves by intrinsically limiting their own capacities of survival. Thus, biological containment was offered—and continues to be offered—as an adequate means of governance, even in the absence of specific biotechnical tools that could achieve its promise in practice*" (Hurlbut, 2018).

A low risk organism is one that cannot propagate or transfer the underlying causes of an adverse effect. For example, the strains of *Escherichia coli* that have nutritional dependences (called auxotrophic strains) are used to develop recombinant DNA molecules because if the recombinant bacteria were to inadvertently escape a containment facility, they would be uncompetitive and die quickly, thus extinguishing the risk of harm.

This notion is not wrong. Under nutrient limited conditions, their numbers dwindle. However, there is also a certain glibness to the certainty that use of such strains makes the experiment "essentially zero risk", if auxotrophy is the or a partial basis for the claim.

The effectiveness of the mitigation, and the certainty of outcome, are both conditional rather than absolutes. Starvation conditions are not ubiquitous outside of the laboratory. Sharing of nutritional resources is more common than appreciated (Pande et al., 2014). Auxotrophic *E. coli* can be more fit than nutritionally self-sufficient strains in environments where the missing nutrient is plentiful (D'Souza et al., 2014; D'Souza & Kost, 2016). "Our results demonstrate that both the genetic background and environmental conditions determine the adaptive value of a loss-of-biochemical-function mutation…" (D'Souza et al., 2015).

In evolution, there are few absolutes and many uncertainties. This understanding should warn policymakers away from overconfident predictions made by technical experts.

[Some references are open source.]

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Proposal 1.1: Biosafety committees.

Response 6: **Yes, with qualifications**.
Response 7: **Yes**. Application of the distributed biosafety committee approach in a critical control points framework.

We agree that the proposed Biosafety Committees could work within either the proposed tier-risk or critical control points framework if properly formed, managed, and coordinated. Our concern with the EPA accreditation and post-hoc annual review is that errant decisions will become embedded practice either at the associated institution or by precedent and recalcitrant to correction.

Moreover, in order to meet the objectives, the review of decisions by Biosafety Committees must extend to authentic verification of biosafety operational compliance post decision. This may be done by MPI (as is the case now), EPA, or another independent registered and *liable* external organisation.

1. Biosafety Committees should be formed under the concept of a PCBU as used in the Health and Safety at Work Act (2015) with members and the chief executive, at least, being officers.
2. Biosafety Committees must have a minority of members who are dependent upon the Biosafety Committee determinations at any workplace.[17] At least some members should be external to and independent of the institution. There must be authentic Māori voice made possible by remuneration. External members also should be remunerated. Internal dissent must be recorded in the minutes of the meeting, even if dissenting views do not prevail.
3. No Biosafety Committee should be forced by the EPA or another Biosafety Committee to issue an approval for work that it has determined could not be safely conducted at its institution. Approval at one Biosafety Committee or EPA does not override a rejection by any other institutional Biosafety Committee.
4. Decisions made by an accredited Biosafety Committee should be provisional until validated by the annual EPA review. This would not prevent work from commencing, but work may be reclassified or halted after the review.
5. It may be appropriate for decisions made by an accredited Biosafety Committee to transfer to any other institution with an accredited Biosafety Committee provided that the other institutions can meet the necessary conditions for the approval.[18] Approvals of this kind should be reviewed by the secondary Biosafety Committee when activated at the institution.
6. It must be possible for different Biosafety Committees to come to different conclusions even if respective institutions could meet the necessary conditions for approval. When this degree of uncertainty over risk exists (or becomes known), any decision already made must remain or be reverted to provisional until reviewed by EPA.
7. There must be penalties for EPA, institutions, and committees that are not meeting expectations or legal obligations. These penalties must apply at an executive level to ensure that the penalty is not transferred back to the public. Examples of penalties are suspensions of authority to make decisions, personal liability for managers, revoked decisions.

[17] Those stakeholders can be heard through applications or invitation for technical advice.
[18] This has the added benefit of providing employment mobility to personnel.

Proposal 2: Reduce the assessment and approval requirements for medicines that are, or contain, new organisms.

Response 8: **Yes**.
Response 9: **Yes**. No other issues special to this proposal.
Response 10: **Yes**, a critical control points framework.

Please see extended responses to Proposal 1 and 1.1.

Proposal 3: Replace current record-keeping requirements.

Response 11: **Possibly**. We would in principle support the labelling and record keeping changes but not in conjunction with adoption of either Proposal 1 risk-tier 1 or Proposal 7.
Response 12: **Yes**.
Response 13: **Not entirely**. The proposed changes would only apply to containment facilities that are approved by MPI. This would result in new organisms that were not recorded or traceable when made in a facility under risk-tier 1 that was not MPI approved, or any GMO that gained new status by transferring to the non-GMO Regulations. We cannot reconcile this with the Minister's statement that he is *"not looking to change the rules related to field trials and releases of GMOs into the environment."*
Response 14: **No response**.

Proposal 4: Adjust internal audit frequency to be proportionate to risk.

Response 15: **Yes**.
Response 16: **Yes**.
Response 17: **No response**.

Proposal 5: Adjust the requirements for the movement of new organisms to be proportionate to risk.

Response 18: **Yes** to transport between PC-rated facilities.
Response 19: **No** for transport of risk-tier 1 organisms or de facto GMOs moved to the non-GMO Regulations.
Response 20: **Yes**. Withdraw the proposed tier-risk 1 category of GMOs and Proposal 7.

We see no substantial savings between the proposed requirements for risk-tier 1 GMOs and GMOs that must be contained at PC1. Furthermore, because the Ministry has not defined a laboratory suitable for risk-tier 1 work, the sending requirements could be more stringent than the standards of either the sending or receiving laboratory.

Proposal 6: Reduce regulatory requirements for the use of eukaryotic somatic cells.

Response 21: **No**. We do not support risk-tier 1 as presently proposed so could not support this Proposal.
Response 22: **No to all**.
Response 23: **Yes**. Withdraw the proposed tier-risk 1 category of GMOs and Proposal 7.

We have elaborated reasons for not supporting risk-tier 1.

The Proposal should be reduced to: Reduce regulatory requirements for the use of animal cells.

We agree that "The cells or tissues must not include human embryonic stem cells, germ cells, oocytes, zygotes or early embryos." However, this condition should apply to these cells of *all* animals.

The preponderance of plant and fungal cells are totipotent (Money, 2002; Su et al., 2021). Under the proposed condition that the "plant cells or tissues [and fungal and animal cells or tissues] cannot spontaneously generate a whole [organism] and cannot be regenerated into a whole [organism]", we see no substantive value in the inclusion of plants and fungi in Proposal 6.

Stringent exclusionary criteria would need to be introduced including definitions of somatic cells that prevented them from forming or establishing in another organism.

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Proposal 8: Reduce assessment requirements for low-risk fermentation.

Response 28: **No**. We could agree to the proposed changes from risk-tier 2 and higher.
Response 29: **No**.
Response 30: **Yes**. Withdraw the proposed tier-risk 1 category of GMOs and Proposal 7.
Response 31: **No response**.

We have elaborated reasons for not supporting risk-tier 1.

Proposal 9: Maintain or adjust the approach to standards for containment facilities.

Response 32: **We have no preference**, provided that all meet the purpose of the Act.
Response 33: **No response**.
Response 34: **No response**.
Response 35: **No response**.

Proposal 10: Require regular reviews of regulatory settings

Response 36: **No**.
Response 37: **No**.
Response 38: **No**.
Response 39: **Yes**.

Proposal 10 in the context of Aotearoa's regulatory environment would be an incremental escalator to deregulation of GMOs. The present regulatory environment, as we have indicated earlier, is far too tuned to industry and institutional voices. Privileging the technical-commercial community (including the Crown Research Institutes and entrepreneurial universities) has dire consequences for the social contract.

On a five or ten year cycle of review, the already privileged community would have greater access to the Ministry building up an even larger gap between the many stakeholder publics and the loudest and best resourced sub-public that has a stake in gene technology.

Proposal 10 would seem less confronting if the Ministry had adopted a more mature methodology for consultation. The Ministry should also be cautious about taking the opinion of professional bodies at face value. They so far demonstrate little skill in developing policy from a multidisciplinary process, or indicate that they are ready to work with disagreement and dissent.

We have previously emphasised the social science research literature for Responsible Research and Innovation (RRI) and similar approaches (Agapito-Tenfen et al., 2018; Foley et al., 2016; Roberts et al., 2020). Implementation would be assisted by a reflexive analysis (Montenegro de Wit, 2020; Saltelli et al., 2020). A useful starting point is Saltelli et al (2020) and their six lenses of post-normal science, controversy studies, sensitivity auditing, bioeconomics, ethics of science for governance, and non-Ricardian economics.

We would also suggest that if the HSNO Act is to be reviewed, a prime candidate for review is the latitude of HSNO Committee decision-making and the boundaries between interpreting the legislation and amending legislation through regulations.

[Some references are open source.]

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