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Submission on Proposal P1055 Definitions of Gene Technology

Lay summary

INBI supports the effort to define gene technology in a way that captures all current and future techniques. However, the proposed preferred definition is inadequate. In addition, we note that Australia has already defined some techniques as not gene technology despite their potential conformity to FSANZ's preferred definition.[1] *We are therefore concerned that any definition is* pro forma *and without substance.*

We do not agree that a priori *exclusions based on hypothetical and voluntary evaluations of biological characteristics of some New Breeding Techniques products are sufficient to ensure safe and responsible use of gene technology.*

We propose that this is an opportunity to adopt both a risk-relevant definition and a risk assessment framework that is risk-relevant by moving away from a list of arbitrary and mutable technical terms based on named examples of gene technology and onto a critical control points framework. The goal should be a regulatory system that is no less safe rather than not more complicated. With changes in technology FSANZ cannot expect that risk assessment gets simpler.

Summary

The intention to re-define gene technology for legislative purposes is welcome. Gene technology requires a definition that is responsible to the valid societal expectation that it can be used responsibly because the potential for harm can be maintained at an acceptable level.

Unfortunately, the proposed definition is of a genre that will suffer the same premature aging as the current definition. A new definition should describe the activities of gene technology that relate to the risks it creates, not rely upon the assumption that underlying biological terminology has the same meaning to everyone. We submit that FSANZ should consider what makes gene technology a technology and look to regulate gene technology with lessons from the successful use of critical control points for other technologies. With the adoption of a future-ready and scientifically-consistent definition we believe that it is possible to group uses and products according to categories that are defined by the critical control points that determine when and what risk assessment is needed.

[1] "techniques that use recombinant, synthesised or amplified nucleic acid to modify or create a genome"

We thank Food Standards Australia New Zealand for inviting responses to this proposal.

As we understand the proposal, FSANZ is seeking to revise the definitions of gene technology in order to 1. improve regulatory clarity on what is and is not within scope, 2. remain able to regulate already recognised techniques and adapt as techniques of genetic engineering are described in novel new ways or when eventually fundamentally new techniques may be invented, and to 3. organise products into risk groups that allow for case-specific, efficient and effective risk assessment. **The Centre for Integrated Research in Biosafety (INBI) supports these *objectives***.

FSANZ understandably wants to future-proof the legislation and regulations. To do so requires describing the technology through the fundamental characteristics that define why it should be regulated and how to control its potential to cause harm. Unfortunately, the analysis provided in Proposal P1055 does not do this but instead continues to use a list of examples in a semantic approach for grouping techniques of gene technology. P1055 persists in the failing approach of using undefined words that keep on morphing in meaning, both through scientific advances and because some developers and researchers want to limit their meanings to maximise deregulated space, which also minimises accountability for harm.[2]

To future-proof legislation and regulations requires a vision for scope that covers how genetically modified organisms are presently made and how the technology is changing how they can be made. Describing techniques of gene technology by their biochemistry, whether it be the reactions that lead to the insertion of a 'transgene' and the reactions that lead to genome editing, provides little clarity for technology governance.

The difference in the scales at which different techniques and products can be used matters for governance.[3] *The characteristic of the technology that justifies social governance through legislation is that it can amplify the rate and magnitude of harm by increasing the ease of use, number of people using it, range of types of organisms and numbers of individuals it is used on, and the number of environments where it can be applied.* Every technique of gene technology invented does this relative to conventional breeding, which is scale-limited by the rate of spontaneous genetic change that can be acted upon by breeders and the generation time of the organisms that they breed.

Chemical and radiation mutagenesis changed the rate of genetic change. *In vitro* mutagenesis using chemicals or oligonucleotides increased the efficiency of creating desired changes. Transgenesis further increased the rate of genetic change as well as efficiency of creating desired changes. The "New Breeding Techniques" accelerate change by also increasing efficiency but also through easier access to the reagents and reducing dependence on highly trained personnel and expensive facilities (Heinemann et al. 2021).

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[2] For example, see the tortured attempt by COGEM (COGEM 2010) to find a way to define recombinant and failure to achieve any scientific basis. Similar arbitrary and inconsistent reasoning is used to define epigenes out of scope. Likewise, protein-nucleic acids (PNAs) and future chemicals derived from modified nucleic acids may be arbitrarily defined as different from what the proposed regulations mean by nucleic acids.

[3] For plain English summaries of this point, see: https://theconversation.com/calling-the-latest-gene-technologies-natural-is-a-semantic-distraction-they-must-still-be-regulated-166352 and https://abiggerconversation.org/genetic-technologies-safety-and-risk-correlate-with-scale-not-naturalness/.

The new dimensions of scale available to NBTs include among other things a new pipeline for changing characteristics of organisms that are food, or are inseparable from our food. For example, genome editing reagents can be applied as topical agents absorbed on contact, in the digestive track or in lungs by inhalation. They can be used to create desired genetic changes in real time over landscapes or product types, even in the grocery store (Heinemann 2019; Heinemann and Walker 2019).

The model underlying P1055 is one where expensive laboratory facilities with highly trained personnel are needed in order to create, identify, and then amplify a rare modified individual. As a consequence, the developer secures a pure stock. Well before release into the environment or use in food, the characteristics of the organism are described.[4,5] This is the history of all the products upon which FSANZ has based its analysis in P1055. Extrapolations to future-proofed regulation cannot be made from that history. The potential exists for all techniques of gene technology and associated new methodologies to increase the potential for any of them to cause harm if arbitrarily released from active regulatory oversight.

A technique can be defined out of scope but not as safe. We submit that FSANZ should focus on the characteristics of technology that create risk and manage those characteristics with risk assessment and other means, as appropriate. This would be a departure from the focus on how techniques, biochemical reactions, genes, genomes and biological characteristics can be described to sound more or less like something not made using gene technology.

1. Governance and legislative scope

    1.1. What FSANZ refers to as a "legal definition for GM food based on old methods" is not accurate.[6] The techniques referred to as NBTs are neither new techniques nor are they new to food produced using gene technology. When the legal definitions were adopted, there had been for decades tools for guided or site-directed DNA modifications, the feature all described NBTs have in common (Heinemann et al. 2021). Indeed even the term "gene editing" was used in a 1980 review of contemporary techniques of genetic engineering (Itakura and Riggs 1980). There are documented cases of editing using oligonucleotides unassisted by nucleases (such as Cas9, which is a new *catalyst*) in the late 1980s and early 1990s in both yeast and mice (Heinemann et al. 2021).

[4] However, the difference between the current pipeline of making an organism in containment and assessing its characteristics prior to release or use as food and *in situ* use of the NBTs is a critical control point that is relevant to what categories products would fall into for risk assessment. Thus, not the NBT used but controls on where it is used prior to evaluation would be the important regulatory trigger.

[5] The techniques of genetic engineering have long been scale-limited by the need to use contained laboratories to protect and find the rare individuals that have been altered by the techniques *in vitro*, which is partly because of the inefficient uptake of exogenous nucleic acids, even transfer from *Agrobacterium tumefaciens*, and proteinaceous mutagens such as double-stranded DNA nucleases (Heinemann et al. 2021). These methodological constraints result in a development paradigm where individual GMOs are amplified in containment and then in pure form are analysed for a pre-market risk assessment. Not all anticipated applications of NBTs are similarly constrained and therefore do not result in a single, pure GMO from which it is possible to credibly assert similarity of biological and chemical characteristics (Heinemann and Walker 2019).

[6] From the FSANZ consultation documents. "New breeding techniques or NBTs are a diverse collection of new techniques for genetic modification that have emerged over the last decade or more."

1.2. We acknowledge that routine use of site-directed tools in plants and livestock animal species was limited prior to the development of, for example, ZFNs, TALENs and CRISPR/Cas. However, oligonucleotide mutagenesis was available for use. This is not to say that creating genetically modified organisms in these species using such reagents was easy, and that perhaps is why the 'transgene' methods dominated for use in agriculture over those decades. However, it is inaccurate to say that in general NBTs are based on fundamentally new methodologies. Calling them new does not make them new.

1.3. One NBT that might be new is the use of double-stranded RNA to cause temporary or heritable changes in gene expression (usually gene silencing) or to cause recombination with heritable RNA elements, such as found in fungi (Heinemann 2019).[7] However, it is a site-directed nucleic acid technique as are other NBTs.

1.4. Therefore, **we agree with the proposal to** "revise and expand the process-based definition for 'gene technology' to capture all methods for genetic modification other than conventional breeding". This should include both chemical and radiation mutagenesis and gene silencing if for no other reason than in the latter technique the double-stranded RNA can recombine with heritable RNA elements in fungi and it can in some organisms cause heritable changes (Heinemann 2019).

2. How to categorise for risk

2.1. In general **we agree that**:

2.1.1. NBTs may result in foods with *biological and chemical* characteristics similar to those that arise from spontaneous processes in nature that are then amplified under a supervised process such as conventional breeding, and that NBTs may result in foods that do not have similar biological and chemical characteristics.

2.1.2. NBT foods can be regulated "in a manner that is commensurate with the risks they pose."[6]

2.2. **We do not agree that** similarities in biological and chemical characteristics are sufficient to determine safety without a risk assessment. While some of these changes will not result in adverse effects, a compulsory pre-market risk assessment helps to reduce the chances that those that could cause adverse effects will enter the food system. Deregulation of any technology potentially grows its scale of use and diversity of users. The more who use gene technology, the more likely an adverse event or product will arise. Risk but not safety scales with deregulation.

2.3. Not all applications for approval of GM foods received by FSANZ and other regulators around the world have either been accepted or progressed to a stage of regulatory compliance. The pre-market risk assessment may be a - or the - reason why there is no definitive proof of a harmful GM food approved by regulators so

[7] We find it mildly curious that while this truly new technique with no history of safe use conforms to FSANZ's preferred new definition of gene technology – "techniques that use recombinant, synthesised or amplified nucleic acid to modify or create a genome" – it is specifically defined by Australia as not gene technology.

far.[8] In the following paragraphs we provide examples of how regulation constrains the scalability of harm.

2.3.1. Two foods with the *same* biological and chemical characteristics can have *different* potential to cause harm. This is due to the differential caused by social/legal conventions that determine what, if any, kind of intellectual property rights they attract. For example, NBT products can be granted intellectual property rights protections that are more powerful than products that have been isolated by conventional breeding despite being judged to have the same biological and chemical characteristics. The stronger the IPR, the greater the likelihood the product will be favoured by the mega-concentrated food production and distribution industries. Consequently, any undetected harm could be more quickly and widely amplified and distributed by products made using NBTs than those conventionally breed. They may also undergo different pre-sale processing resulting in different chemical reactions and further disconnecting them from the history of safe use.

2.3.2. Without a risk assessment, the number of biological and chemical characteristics that are different is likely to be underestimated because only characteristics related to intended or anticipated changes will be examined. Even if an unbiased screen were routinely used, the public cannot be assured that an 'apples and ~apples' approach to comparator selection was used. For example, FSANZ has previously used a characteristic of button mushrooms to argue the equivalence with a characteristic in a GM maize despite the many characteristics, including consumption patterns and food preparation, that are different between conventional mushrooms and maize.[9]

2.3.3. Deregulation may result in even more egregious examples of cherry picking characteristics of different varieties, and sometimes very different species, for comparison purposes.

2.3.4. Importantly, all comparisons lead to normative judgements, not absolute certainty of safety. How similar is similar? How many characteristics have to be similar for overall biological and chemical similarity? Different standards may exist between regulators as well as between manufacturers. The US National Academies warns us of the embedded uncertainty even in rigorous assessments.

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[8] For example: "In the first case, research was conducted on a soybean line genetically engineered to produce a Brazil nut (*Bertholletia excelsa*) protein, which was a known allergen. Sera from patients allergic to Brazil nut protein were available and tested positive for activity against the GE soybean protein. Because the segregation from the human food supply of GE soybean with that protein could not be guaranteed, the project was halted (Nordlee et al., 1996). The soybean variety was never commercialized" (NASEM 2016). Note that the original publication reported that the gene for the protein had already been inserted also into "tobacco, oilseed rape (Brassica napus), the legume Vicia narbonensis, and beans (Phaseolus vulgaris)" (Nordlee et al. 1996). "As a result of this assessment, commercial interest in this transgenic soybean variety was abandoned. However, we stress that such e*xperiments in the hands of no[n] experts* may pave the way to new mishaps" (emphasis added to quote from Cantani 2006).

[9] https://www.researchgate.net/publication/271206465_Submission_to_Food_Standards_AustraliaNew_Zealand_on_A549_High_Lysine_Corn_Draft_Assessment_Recommendation

This uncertainty is not adequately addressed in proposals to exclude some products from regulatory oversight.

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. (NASEM 2016)

2.4. To regulate a technology *proportional* to risk requires knowing how the harm can scale. This knowledge may seem easier to obtain for food than for environmental risk assessment, but that is not assured. For example, different home preparation traditions including different mixtures of foods contribute to the complexity of assessing risk. Recalling the quote above by the US NASEM which acknowledges the uncertainties that characterise the science, "[p]roportionality can only be relevant to what is reliably known and quantifiable (i.e. due to case-by-case basis); the possible adverse effects of genome edited [NBT] plants are far from reliably knowable, including risks through scaling and across time."[10]

2.5. Nevertheless, provided that FSANZ were able to confirm that those using NBTs on food have completed a credible examination of the product for unintended changes *and* associated unintended biological characteristics, it is theoretically possible to place some products into different categories with different assessment requirements.

2.5.1. Disappointingly, this theoretical possibility is already undermined by the industry itself. An "argument in favor of equivalence testing is that the onus to do high-quality, well-replicated experiments with sufficient statistical power is placed on to those who wish to demonstrate the safety of GMOs" (van der Voet et al. 2019), but it also incentivises cheating, or at least sloppiness. The most recent demonstration is that of Recombinetics' cattle. Following the company's publicly expressed confidence in its approach to screening unintended changes it was later found to have overlooked unintended transgene insertions. The industry has not yet earned the trust society can expect of a regulator relying on voluntary compliance.

The developer of hornless cattle has retracted its claims about precision and purity of the genome modifications (Carlson et al., 2016; Van Eenennaam et al., 2019) after FDA scientists found that they were not accurate (Norris et al., 2020). The company initially said that: "We have all the scientific data that proves that there are no off target effects" (quoted in Regalado, 2020), but it overlooked, among other changes, about 4,000 new

[10] European Network of Scientists for Social and Environmental Responsibility
https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13119-Legislation-for-plants-produced-by-certain-new-genomic-techniques/F2743463_en

nucleotides inserted during the application of the new techniques, including antibiotic resistance genes. (Heinemann et al. 2021)

2.5.2. Unfortunately, we also see little evidence from the history of FSANZ that without legislative or political compulsion it will use its own discretion to improve the reporting standards from manufacturers. For example, it does not require the use of techniques that provide comprehensive identification of unintended changes in its risk assessments despite this being a recommendation from both the research community (Agapito-Tenfen et al. 2018; Heinemann et al. 2011) and the US National Academies:

It is the change in the actual characteristics of the plant, intended and unintended, that should be assessed for risks. Recent developments in -omics technologies have made thorough assessments of those characteristics of plants attainable in the near future. Even in their current state of development, the technologies could enable a tiered approach to regulatory testing in which any new variety shown to have no new intended traits with health or environmental concerns and no unintended alterations of concern in its composition would be exempted from further testing (Figure S-3). The costs of -omics methods are decreasing, but even current costs are low relative to the cost of other components of regulatory assessments. (NASEM 2016)

2.6. For these and other reasons (set out below):

2.6.1. **INBI does support** (Option 3) a "revised and expanded process-based definition for 'gene technology'". **We do not support** the definition that FSANZ prefers.

2.6.2. **INBI does not support** "Product-based pre-market safety assessment exclusions for certain foods" based on exclusion criteria focussed on food characteristics alone. We do not believe that the proposed non-regulatory approaches are a satisfactory way to mitigate risk.

2.6.3. *We submit that the proposed product-based exclusions are actually process-based exclusions in disguise.* FSANZ is proposing to deregulate processes that result in products that have characteristics similar to other products that may have been created using arbitrarily deregulated processes, for example chemical and radiation mutagenesis or heritable double-stranded RNA treatments, and never assessed for risk. The product-based exclusion is therefore likely to lead to risk creep.

2.6.4. **INBI supports** Option 3 with the deletion of the sentences "revise the definition for 'food produced using gene technology' to include specific product-based criteria for excluding certain foods from pre-market safety assessment and approval as GM food. Foods not meeting all relevant exclusion criteria would require an application to FSANZ." Those sentences could be replaced with "Foods produced by NBTs require an application to FSANZ."

3. Product-based voluntary approaches are not future-proof

3.1. This quote from a submission to the European Commission on its consultation on regulation of new techniques demonstrates precisely the same problem with FSANZ's framing of risk. "Several OECD countries including Canada, the US, Japan, Australia, and Colombia are adopting similar, pragmatic approaches. At their base, they recognize that new genomic techniques are no riskier than conventional breeding and therefore should be managed accordingly."[11]

3.2. In contrast, the Norwegian Society of Rural Women frame the risk appropriately by saying: "We are not against GMOs in general, but genetic engineering differs from traditional breeding and processing in both radicalism and pace."[12] This is similar to Nobel Laurette Sydney Brenner's framing when he said that (radicalism) "there is now available a method which allows us to cross very large evolutionary barriers and to move genes between organisms which have never before had genetic contact" and (pace) the "essence is that we now have the tools to speed up biological change and if this is carried out on a large enough scale then we can say that if anything can happen it certainly will. In this field, unlike motor car driving, accidents are self-replicating and could also be contagious" (Brenner 1974).

3.3. Conventional breeding is limited by the spontaneous mutation rate, generation time of the organism, species, size of the organism, power of applicable intellectual property rights instruments, and number of breeders. NBTs have far fewer limitations. Their difference in radicalism and pace is, after all, why they have value and concomitantly how they can cause harm.

3.4. The fundamental characteristic of technology is that it allows people to do things faster and in a more concentrated way (Heinemann et al. 2021).[3] The fundamental source of harm from technology is that people can do certain things faster and in a more concentrated way. Deregulation increases the number of people using the techniques and lowers the expertise required to use them. Therefore, the reason to regulate technology is to control the potential for harm from its use by people. A focus on products of a technological process is a way to control harm from a technology but it is not the only way.

3.4.1. For example, chemical and radiation mutagenesis is a technology because it allows changes to be made to genes and organisms faster than what occurs by conventional breeding, the latter relying on the spontaneous mutation rate. The use of chemical and radiation mutagenesis is considered a gene technology in

[11] Submission to the European Commission on its consultation Legislation for plants produced by certain new genomic techniques by the Canadian Canola Growers Association (Janelle Whitley) 22 October 2021. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13119-Legislation-for-plants-produced-by-certain-new-genomic-techniques_en

[12] Norwegian Society of Rural Women https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13119-Legislation-for-plants-produced-by-certain-new-genomic-techniques/F2743498_en
European Network of Scientists for Social and Environmental Responsibility
https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13119-Legislation-for-plants-produced-by-certain-new-genomic-techniques/F2743463_en

the European Union and New Zealand, but organisms made using these mutagens are (mainly) exempted from regulation (DoH 2018b). In 2006 Australia defined chemical and radiation mutagenesis as *not* a gene technology (DoH 2018a).[13]

3.4.2. The decision to define chemical and radiation mutagenesis as not a gene technology but transgenesis and NBTs as gene technology is scientifically inconsistent. It exposes a lack of understanding of the underlying purpose of regulation to control adverse effects of technology. The impact of doing so is, however, limited. This is not because chemical and radiation mutagenesis has no scalable potential to cause harm. It is because the reagents of chemical and radiation mutagenesis are controlled by other legislative instruments that restrict access and require that they be used by highly trained personnel in containment facilities, and require registration of the products (Heinemann et al. 2021). P1055 does not create these other controls for NBTs.

3.5. We do not believe that it is valid to compare what can be done using technology to the history of spontaneous DNA changes that have occurred in the genomes of organisms people eat over evolutionary time. First, *both* people and food have been changing over evolutionary time. Mutations that arose spontaneously in nature resulted in foods that may have been better, worse, or irrelevant to us. Our genetic ancestors may also have evolved (genetically or through learning) to overcome the effects of mutations that lessened the value of these organisms to us as food. Second, foods produced using gene technology do not have evolutionary time lines. Our highly concentrated food industries can inadvertently distribute something harmful to large numbers of people in a short time unlike at any other period in human evolution. *Consequently we disagree with the conclusion that "Conventional food is therefore a suitable benchmark for assessing the risks from NBT foods" or other gene technology techniques.*

3.6. FSANZ knows how little product it takes to contaminate the world food supply with unapproved and therefore potentially unsafe food, which is why it no longer issues split decisions with the Office of the Gene Technology Regulator. On the global scale, production of Starlink and BT10 maize, LL rice, and Roundup Ready wheat were miniscule. In some cases, only a few hectares. Yet these products spread worldwide and a few, decades later, are still appearing. Even the scale of small scale tinkerers becomes relevant to food safety. The worrying message from adoption of P1055 is that tinkering is safe because the process is safe.

3.7. P1055 is not addressing non-genetic risks to food safety. Risk is also a function of the concentration of the food production and distribution sector and its capacity to

[13] Why Australia took this decision is not apparent to us. Proposal P1055 is a way to rectify this inconsistency provided that it could be made inclusive of specifically deregulated gene technology techniques. If regulatory expediency were the reason it was defined out of legislation, clearly that was not the only option because as proposed in P1055, organisms made using chemical or radiation mutagenesis could be exempted from further risk assessment rather than use arbitrary exclusions. We note that New Zealand has defined some chemical mutagenesis as and some as not creating a GMO for purposes of risk assessment.

use monopoly power intellectual property rights – that conventional breeding has not had – to ramp-up harm at unprecedented scale. If conventional foods were a suitable benchmark for assessing the genetic risks from NBT foods (which we do not accept), then FSANZ should consider that *infectious disease* (see Brenner's quote, above) *is the other appropriate benchmark for assessing the modern risks from NBT foods.*

3.8. Deregulation is *de facto* scale change in the mutation rate of both food and inseparable organisms that occur in food.[14] The scale is increased in magnitude by the number of people who use the tools and the number of organisms exposed. That number can and will increase with products that allow such work *in situ*, through topical applications (Heinemann and Walker 2019). In the proposed product-based and voluntary compliance framework proposed, only the intended food organisms will be evaluated. How many off-target effects of the inseparable fungi inadvertently sprayed with a ZFN or a Cas9-guide mixture intended as a herbicide on a "farm" of 10,000 hectares is FSANZ suggesting that society accept as safe without review?

3.9. We offer a potential solution to this problem by suggesting that it is not the technique of gene technology used that is determinative of the risk category. In the first instance it is *how* the technique is used. We present that idea below but with this caution. The intention of FSANZ may be to reduce the use and expense of risk assessment, but that would only be possible if the technology had not changed. Obviously, it has at least in its ability to scale. Therefore, as the US NASEM observed, risk assessment may need to change for safety to stay the same or improve.

"[f]uture GE crops…could greatly expand the use of agricultural biotechnology in the development of biofuels, forestry restoration, and industrial bioprocessing and thus potentially lead to new risk-assessment and risk-management issues." (NASEM 2016).

3.10. Exclusion criteria are not supported by us. However it may be possible to group uses into categories defined by relevant critical control points. Two examples follow.

3.10.1. A risk assessment category might apply to all development done in containment and all development that was from chemical and radiation mutagenesis. This category could include all genetically engineered livestock and plants of the kind that already have been approved by FSANZ, and could apply to all future development using NBTs this way. For practical purposes, the members of this category could be split into sub-categories for risk assessment. In category 1A are the products of chemical and radiation mutagenesis that require no further assessment provided that they were also listed with the International Atomic Energy Agency. This is because of other regulatory restrictions on the use of chemical and radiation mutagens. In category 1B are all other products that will be evaluated according to the requirements of law and to evolving standards of international guidance, such as *Codex Alimentarius*. Proposals for this should be developed and consulted by FSANZ, but we also

[14] For example, microorganisms and bits of insects.

encourage adoption of -omics based techniques for hazard identification as recommended by the US NASEM.

3.10.2. A different risk assessment category might apply to any outdoor use of gene technology and to release of Living (genetically) Modified Organisms. Therefore, it may require thorough and new approaches to risk assessment and risk management which should be developed and consulted by FSANZ. However, it may also be possible to further sub-categorise members of this set with case-specific assessments.

4. Definition criteria

4.1. The USDA definition preferred by FSANZ is inadequate to cover some current and also future/pending techniques or actually new technologies.

4.2. The length of the definition in Australian (and New Zealand) legislation as listed in Table 2 of Supporting Document 3 illustrates the failures of its semantic approach to defining gene technology. Australia has already inconsistently defined some techniques as not being gene technology despite them potentially conforming to the USDA definition. Thus, we do not believe that the USDA or any other definition based on other undefined/contested terms either will be sufficient or future-proof.

4.3. Instead, we advocate a heuristic definition that describes the properties of gene technology. We submit that a new draft definition should be developed for further consultation.

4.3.1. The definition *should not* exclude technology that increases the scale of potential harm with use.[15]

4.3.2. The definition *should not* be limited to nucleic acids. The use of any agent intended to accelerate the overall or specific mutation rate and rate of creating new phenotypes should be included.[16] It is unclear why only one kind of agent (nucleic acids) for introducing genetic change is identified by FSANZ as relevant when the biological and other risks are the genes that are changed.

4.3.3. The definition *should not* be limited to the persistence of the causative agent, nucleic acid or otherwise, in a product for the product to be within scope.

[15] Advancements in nucleic acid delivery also allow proteins to be taken up *in situ*, including proteins that may have mutagenic activities (Heinemann and Walker 2019). In this continuum resides what is commonly understood to be genetic engineering, but does not necessary require the "use of recombinant, synthesised or amplified nucleic acid to modify or create a genome" because of arbitrary definitions also used in practice for the words "genome", "recombinant", "amplified" and "synthesise" as well as the ability to substitute other kinds of molecules for nucleic acids to achieve the end result. Spraying protein mutators such as ZFNs or TALENs in a formulation that allows them to be taken into cells can have the same outcome as spraying small chemical mutagens or radioactive material. The latter is prevented by other legislation because of potential to cause harm (Heinemann et al. 2021). The same potential harm should be recognised for mutagens that are proteins or other non-nucleic acid molecules.

[16] Note that treatments to alter traits en masse by manipulating genes is a pathway of scalable harm for long lived perennial plants and even fresh fruits and vegetables post-harvest, even if the organism does not reproduce (Heinemann 2019).

4.3.4. If the word genome is to be used, then it should be defined in a way that is comprehensive for any molecular basis of inheritance of traits because inheritance is a pathway to scalable harm. We should not, for example, be arguing in the future about whether or not making changes to replicating RNA elements in the cytoplasm of fungi is genetic engineering because of semantic disputes over whether or not they are part of the "genome".

4.3.5. The definition *should* capture all technology that can result in the change of biological or chemical characteristics, phenotypes/traits by intervention in the pathways and molecules that determine the biological or chemical, phenotypes/traits of organisms, viruses and other replicating elements (e.g., plasmids, prions and epigenes). We should not, for example, be arguing in the future about whether or not making life-long changes to gene expression in fruit trees by application of double-stranded RNA is a gene technology.

Nāku iti nei, nā,

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[17] This submission and any accompanying documents are provided in accordance with the University of Canterbury Critic and Conscience of Society and Academic Freedom Policy (2018) as the author's expert opinion and not as statements of the opinion of the University of Canterbury. It was externally reviewed by an expert in the field.

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