gene ethics
working for a GM-free future

[redacted]

November 8, 2023

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Re: comments on A1274 – GM cavendish banana

Dear FSANZ Team:

Thanks for the opportunity to comment on this application.

Recommendations

That FSANZ require the A1274 applicants to

- Independently test these Genetically Manipulated (GM) bananas to validate the claims and assumptions that pathogens are unlikely to acquire antibiotic resistance genes from GM plants, in the environment and human alimentary tracts;
- Remove the antibiotic resistance marker genes from this commercial line of GM bananas, as the applicants note they had done so in field trial application DIR146;
- Compile current evidence on the culturally diverse patterns of banana consumption and dietary exposure in the Australian community, to more reliably interpret the findings of report QUT2023-4: Concentrations of MamRGA2 and NPTII proteins in banana fruit and peel tissues from event QCAV-4.

That FSANZ also

- Require the use of safer experimental marker genes to replace the antibiotic resistance and herbicide tolerance markers that still dominate the in vitro selection of GM cells;
- Advocate for a ban on the use of antibiotic resistance genes as selectable markers in the production of GMOs and genome edited organisms of all kinds; and
- If FSANZ approves A1274, empower the governments which Ministers on the Food Forum represent to ensure the labelling requirements for the GM bananas are monitored, enforced and fully complied with, wherever GM bananas are sold.

Introduction

FSANZ confirms

> "There are no fresh GM foods such as fruit, vegetables, meat or fish available for sale in Australia or New Zealand."[1]

So A1274 is a vanguard event that requires FSANZ to treat the application with particular care and precaution. This is the first application to FSANZ for the general approval of a domestically grown GM food that will mainly be eaten fresh, without processing or refining. However, within Australia's diverse cultural communities some banana flesh and skin may be cooked or otherwise processed before eating and the impact of these practices should be assessed.

Bananas are reportedly the biggest selling single supermarket item and Australians eat an average of 16kg per annum. It is important that FSANZ ensure GM banana varieties are safe and it is critical to confirm that they will not wreak wider public health damage on the community.

Other approved GM foods derived from crop plants are highly refined or processed before consumption but bananas are not. As a result, GM bananas may pose more public health concerns, with antibiotic resistance marker genes (ARMGs) remaining in the fruit.

The NPTII gene and the enzyme it codes for are used experimentally as antibiotic resistance marker genes to identify and select GM transformation events in vitro, to select the cells that are modified with the trait of interest. The FSANZ Document notes that NPTII confers tolerance to a number of antibiotics, used to treat a range of diseases. It cites Beck et al. 1982; Redenbaugh et al. 1994; Padilla and Burgos 2010. (4.2 P21) and also the OGTR's Reference Document "Risk Assessment Reference: Marker Genes in GM Plants", to explain that

> "The NPTII gene encodes the aminoglycoside 3'-phosphotransferase II (APH(3')-II) enzyme which confers resistance to aminoglycoside antibiotics, including kanamycin and structurally related antibiotics such as neomycin, paromomycin, ribostamycin, butirosin, gentamicin B, and geneticin that are used in medical treatments."

FSANZ also confirms the significant presence of the NPTII protein in the commercial QCAV-4 lines of the GM bananas proposed for general release on farms throughout Australia, as an antidote to the soil-borne fungal disease fusarium wilt, aka Panama Disease.

> "The NPTII protein is present at average levels of 4.5 ng/mg fresh weight (fw) in peel and 3.1 ng/mg fw in the flesh. A range of characterisation analyses confirmed the identity of NPTII in QCAV-4." (Exec Summary, P ii)

Despite these admissions, FSANZ Document 1, which supports approving the GM cavendish bananas, does not acknowledge that the GM bananas may pose any public health issues that differ from their previous assessments. They dismiss further safety assessments, saying

> "Since the NPTII protein expressed in QCAV-4 has a sequence similarity of 99.6% and is structurally, biochemically and functionally equivalent to the previous NPTII proteins assessed by FSANZ, no further safety evaluation is required other than the examination of updated bioinformatic searches." (4.2.3 P22)

[1] Fact Sheet, GM Foods in Australia and New Zealand
https://www.foodstandards.gov.au/consumer/gmfood/Documents/GM

FSANZ's 'been there, done that' attitude is irresponsible and lacks the precaution required of our regulators. This banana line's potential contribution to the global problem of antibiotic resistant pathogens creating untreatable illnesses in the human population is unacceptable.

The OGTR concedes in its reference document, which FSANZ cites in support of its dismissive attitude, that

> "Although antibiotic resistance genes play no role in the desired phenotypes of the GM plants in the field, … their protein products may directly or indirectly have a negative effect on people and/or animals that consume the plant material."[2]

Neither FSANZ (nor OGTR) have adequately reviewed or assessed the real potential for marker genes remaining in unprocessed foods from GM crops to enter the environment or human digestive systems and to confer antibiotic resistance on pathogens. Nor do the regulators review with sufficient precaution the potential for adverse impacts on human health.

FSANZ should heed much more recent literature than those old and suspect papers which it cites. For instance, this paper notes that

> "Advances in HGT (Horizontal Gene Transfer) detection, aided by next generation sequencing, have demonstrated that HGT occurrence may have been previously underestimated."[3]

Antibiotic resistant pathogens are among the most pressing global public health challenges of our time. Any contribution to the problem, even those regarded as unlikely, must be much more diligently researched, monitored, assessed and treated very seriously. When pathogenic bacteria acquire resistance to antibiotics they can make infections hard or impossible to treat and increase the risk of disease spread, severe illness, and death.

The US Centers for Disease Control and Prevention (CDC) estimate that in that country alone, where most GM foods are grown and consumed, more than 2.8 million antibiotic-resistant infections occur each year, resulting in more than 35,000 deaths. In Australia in 2019, there were 1,600 deaths attributable to anti-microbial resistance (AMR) and 6,700 deaths associated with AMR.[4] Even a 1% contribution to these fatalities should lead to precautionary action.

Antibiotic resistance genes and proteins in GM plants must be treated as a preventable hazard that can be removed before commercialisation. In future, other available and more benign selection markers should be used.

GeneEthics calls for the possible transfer of antibiotic resistance marker genes from GM (and CRISPR genome edited) plants into pathogens to be fully and publicly discussed during the review of A1274. Our concerns should also be influential in FSANZ's decision on the QUT application.

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[2] OGTR (2017) Risk assessment reference: marker genes in GM plants. https://www.ogtr.gov.au/sites/default/files/files/202106/risk assessment reference marker genes in gm plants.pdf

[3] Philips JG, Martin-Avila E, Robold AV. Horizontal gene transfer from genetically modified plants - Regulatory considerations. Front Bioeng Biotechnol. 2022 Aug 31;10:971402. doi: 10.3389/fbioe.2022.971402. PMID: 36118580; PMCID: PMC9471246.

[4] The burden of antimicrobial resistance (AMR) in Australia, Institute for Health Metrics and Evaluation, University of Washington. https://www.healthdata.org/sites/default/files/files/Projects/GRAM/Australia_0.pdf

New robust, independent, scientific research and evidence needed

The NPTII antibiotic resistance gene is approved for wide use as a marker in event selection during GM plant research. Unless removed, as the applicant did in some experiments reported in DIR146, NPTII will remain in every cell of commercial bananas. The public health concern is not the presence of the NPTII gene in GM crops per se, but the potential for antibiotic resistance genes to spread from such a source to pathogenic bacteria in the food supply chain, from seed to stomach and beyond.

The NPTII gene produces enzymes that can confer resistance to aminoglycoside antibiotics in clinical settings. Yet FSANZ (and OGTR) fail to cite the many studies that found genes encoding APH enzymes in various clinical isolates, signifying a real-world impact on the effectiveness of aminoglycoside antibiotics. For instance, Ramirez and Tolmasky (2010)[5] discuss the dissemination of aminoglycoside-modifying enzymes, including APH(3')-II, among bacteria and their impact on clinical outcomes are not cited.

FSANZ (and OGTR) must not ignore or minimise the potential horizontal gene transfer of resistance genes from non-pathogenic to pathogenic bacteria. For example, Wellington et al. (2013) discuss the prevalence of antibiotic resistance genes in the environment and their highly possible capture by pathogenic bacteria. They point to the agency of human actions as

> "The reservoir of resistance genes in the environment is due to a mix of naturally occurring resistance and those present in animal and human waste and the selective effects of pollutants, which can co-select for mobile genetic elements carrying multiple resistant genes. Less attention has been given to how anthropogenic activity might be causing evolution of antibiotic resistance in the environment. … action must be taken to avoid the conjunction of factors that promote evolution and spread of antibiotic resistance."[6]

At least one of those factors which the OGTR (and FSANZ) should take seriously is widespread planting of huge and intensive monocultures of identical GM plants containing NPTII genes.

FSANZ must at the very least reference some of the many papers that question its assumption that horizontal gene transfer from plant materials to micro-organisms is so rare that it does not matter. For instance, FSANZ should consider a 2004 paper that argues

> "Our analysis of antibiotic-resistant bacteria and of the sensitivity of current techniques for monitoring HGT (horizontal gene transfer) from transgenic plants to soil microorganisms has two major implications for field trial assessments of transgenic crops: first, HGT from transgenic plants to microbes could still have an environmental impact at a frequency approximately a trillion times lower than the current risk assessment literature estimates the frequency to be; and second, current methods of environmental sampling to capture genes or traits in a recombinant are too insensitive for monitoring evolution by HGT. A model for HGT involving iterative short-patch events explains how HGT can occur at high frequencies but be detected at extremely low frequencies."[7]

We all live in environments that produce our food so FSANZ must ensure that the foods from those contexts are not toxic or poison in the short term. But the regulator must also ensure they

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[5] Ramirez MS, Tolmasky ME. Aminoglycoside modifying enzymes. Drug Resist Updat. 2010 Dec;13(6):151-71. doi: 10.1016/j.drup.2010.08.003. Epub 2010 Sep 15. PMID: 20833577; PMCID: PMC2992599.

[6] Wellington et al. (2013) The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria, The Lancet, Infectious Diseases, VOLUME 13, ISSUE 2, P155-165, FEBRUARY 2013, https://doi.org/10.1016/S1473-3099(12)70317-1

[7] Heinemann JA and Traavik T., Problems in monitoring horizontal gene transfer in field trials of transgenic plants, Nat Biotechnol. 2004 Sep;22(9):11059. https://pubmed.ncbi.nlm.nih.gov/15340480/

do not compromise the health and wellbeing of the whole population in the longer term, as allowing the conditions under which antibiotic resistant pathogens may emerge clearly does.

FSANZ asserts that

> "The safety of NPTII has been assessed on numerous previous occasions and is well documented in peer reviewed scientific literature (Fuchs *et al.,* 1993)."

But Fuchs, Fraley and other authors were Monsanto employees while others were consultants that Monsanto hired. The company's internally generated experiments used falsified data and findings to promote its GM and agrochemical products. They have been thoroughly discredited[8] yet FSANZ (and OGTR) cite them to reassure the public.

Assuming that all food and its constituents are completely and reliably digested and denatured ignores the evidence that around 20% of Americans, where most GM food is produced and consumed, suffer from digestive conditions.[9] CSIRO reports that in Australia, "At least 50% of Australian adults experience unpleasant gut symptoms such as bloating, gas and constipation, and 1 in 7 experience distressing symptoms."[10]

FSANZ (and OGTR) and the applicants produce no evidence on whether these peoples' gut dysfunction may put them at risk of only partially digesting antimicrobial proteins. They also fail to mention the public health concerns of other government experts such as AURA, that specialises in ameliorating anti-microbial resistance issues here and globally.[11]

Bananas are rich in dietary fibre.[12] CSIRO notes

> "Dietary fibres are essentially non-digestible carbohydrates that are found in edible plant foods. They are resistant to digestion in the small intestine, and are also potentially fermentable, either partially or completely, in the colon."

Even Monsanto recognised antibiotic resistance markers as a potential barrier to commercialising its GM crops, but regulators ignored the threat then too.

> "… in 1999. The company claims that 'responding to public concern, Monsanto is developing alternatives to antibiotic resistance marker genes and methods to remove them. These technologies are in the research stage and are not yet applicable for commercial products.'"[13]

Though Monsanto promised the removal of antibiotic resistance marker genes from GMOs it never delivered. Regulators continue to approve new GMOs that pose the same hazards, risks

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[8] Wisner, Baum. Monsanto Papers. https://www.wisnerbaum.com/toxic-tort-law/monsanto-roundup-lawsuit/monsanto-papers/

[9] Orenstein, P. 9 Common Digestive Conditions From Top to Bottom, Everyday Health December 19, 2022. https://www.everydayhealth.com/digestive-health/common-digestive-conditions-from-top-bottom/

[10] Gut health and weight loss, An overview of the scientific evidence of the benefits of dietary fibre during weight loss, CSIRO January 2019

[11] AURA 2021: Fourth Australian report on antimicrobial use and resistance in human health https://www.safetyandquality.gov.au/our-work/antimicrobial-resistance/antimicrobial-use-and-resistance-australia-surveillance-system/aura-2021

[12] T H Chan School of Public Health, Harvard. https://www.hsph.harvard.edu/nutritionsource/food-features/bananas/

[13] Clarifications Regarding the Risks Posed By The Use Of Antibiotic Resistance Markers (ARMs) in GM Crops And Allegations Reported In The Sunday Times." 1 April 1999, cited in IATP (June 2002 - Antibiotic Resistance and Genetically Engineered Plants) http://biotechknowledge.com/showlibsp/php3?uid=1464 and https://www.iatp.org/sites/default/files/Antibiotic_Resistance_and_Genetically_Engin_2.pdf

and costs of allowing and enabling a contribution to the global scourge of antibiotic resistant pathogens, based on assumptions, data gaps, and weak, compromised evidence.

GM bananas in the human food supply create plausible pathways for antibiotic resistant NPTII proteins to enter the human population. FSANZ must take this public health challenge seriously and reassess its position that the issue is already 'done and dusted'. It is not!

Removing antibiotic resistance marker genes

Section 21 of DIR146, on field trials of these GM bananas, notes that "in some GM banana lines, the *NPTII* gene will be excised using an inducible recombinase system (see Section 5.4.3 for further detail)." Such removal is a good example of the precautionary approach.

We therefore ask the FSANZ to make approval of the commercial GM bananas contingent upon the applicant removing all antibiotic resistance marker genes. As the DIR199 bananas are not scheduled for immediate release, if approved, the QUT research team should have sufficient time to delete all the marker genes from their final crop plants prior to any final approval for general release.

Conclusions

There are alternatives to the antibiotic resistance and herbicide tolerance genes that have dominated the in vitro selection of GM modified cells until now.[14] Provided they are shown to be safe, other methods should be employed for the in vitro selection of GM plant tissues during research and development. The huge public health hazards of antibiotic resistant pathogens globally demands that precaution be exercised. Therefore, the risky and comparatively trivial use of antibiotic resistance genes as selectable markers in the production of GMOs and genome edited organisms must be banned.

If FSANZ approves A1274, empower the governments which Ministers on the Food Forum represent to ensure the labelling requirements for the GM bananas are monitored, enforced and fully complied with, wherever GM bananas are sold.

[14] Didier Breyer, Lilya Kopertekh & Dirk Reheul (2014) Alternatives to Antibiotic Resistance Marker Genes for In Vitro Selection of Genetically Modified Plants – Scientific Developments, Current Use, Operational Access and Biosafety Considerations, Critical Reviews in Plant Sciences, 33:4, 286-330, DOI: 10.1080/07352689.2013.870422