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Department for Environment, Food and Rural Affairs
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Submitted by email to gm-regulation@defra.gsi.gov.uk

27 January 2022

Dear Madam/Sir

Re: Application from John Innes Centre to release a genetically modified organism, reference 21/R52/01 as published at https://www.gov.uk/government/publications/genetically-modified-organisms-john-innes-centre-21r5201

We are writing on behalf of GM Freeze, Genewatch UK, GMWatch, Beyond GM, EcoNexus, the Soil Association, the Organic Research Centre, Organic Farmers & Growers, the Biodynamic Association, the Landworkers Alliance, The Kindling Trust, Whole Health Agriculture, WWOOF UK, the Sustainable Food Trust, GM Free Dorset, GM Free Somerset, GM Free Cymru, Genetic Engineering Network, Agri-Activism UK, Green Christian, Pro-Natural Food Scotland, SE Essex Organic Gardeners, the Springhead Trust, Shepton Farms, The Real Bread Campaign, Bread Matters Ltd and Real Seeds to request that the above application to release genetically modified (GM) wheat is refused.

GM Freeze is the UK umbrella campaign for a responsible, fair and sustainable food system, focused on concerns about the use of genetic engineering in food and farming.

GeneWatch UK is a not-for-profit organisation which aims to ensure genetic science and technologies are used in the public interest. **GMWatch** provides the public with the latest news and comment on genetically modified (GMO) foods and crops and their associated pesticides. **Beyond GM** is an initiative educating and engaging the public to raise the level of debate around the issues of GMOs and sustainable food production in the UK. **EcoNexus** analyses and reports on new technologies that have the potential for significant negative impacts on biodiversity and ecosystems.

The Soil Association is the charity that digs deeper to transform the way we eat, farm and care for the natural environment. **The Organic Research Centre (ORC)** is the UK's leading independent organic research organisation. **Organic Farmers & Growers** were the first UK organic certification body to be approved by the Government and now certify more than half of UK organic land. **The Biodynamic Association** promotes biodynamic methods for healthy farming, forestry and gardening for planet, nature and people.

The Landworkers' Alliance is a grassroots union representing farmers, growers and land-based workers. **The Kindling Trust** works with communities, farmers, health providers, activists and policymakers to create a fairer more sustainable food system for all. **Whole Health Agriculture** is a community of farmers, health professionals and citizens who support and promote those who farm for health and vitality. **WWOOF UK** is a membership charity which connects people wanting to learn about ecological growing and low impact lifestyles with sites across the country. The **Sustainable Food Trust** is a registered charity with a goal of promoting food and farming systems that nourish the health of the planet and its people.

GM Free Dorset is a grass roots campaign promoting rural sustainability across the county of Dorset. **GM Free Somerset** is a grass roots campaign supported by individuals, groups, local businesses and charities that exist to promote rural sustainability. **GM Free Cymru** is the community pressure group campaigning to keep Wales free of genetically modified crops. **Genetic Engineering Network** facilitates the exchange of information between groups and campaigners. **Agri-Activism UK** is a network of people who campaign for cleaner, healthier and more sustainable agricultural and food systems.

Green Christian are inspired by their faith and work to care for Creation through prayer, living simply, public witness, campaigning and mutual encouragement. **Pro-Natural Food Scotland** work to raise awareness about the health benefits of natural foods. **SE Essex Organic Gardeners** is a local group of Garden Organic, supporting and working with the Soil Association and Pesticide Action Network UK. The **Springhead Trust** promotes environmental education, sustainability, organic agriculture and local performing arts.

Shepton Farms are organic farmers and fruit growers. **The Real Bread Campaign** finds and shares ways to make bread better for us, better for our communities and better for the planet. **Bread Matters Ltd** is a bread research and training organisation, run by author of Bread Matters. **Real Seeds** provides open pollinated seed appropriate for growers producing vegetables under sustainable low input conditions.

We do not believe that this trial should go ahead. The applicant has failed to provide key information; the GM plants contain antibiotic resistance genes; there is a risk of escape; and there are significant questions about the value of the project to which the proposed trial contributes. In summary, our objection covers the following points:

1. The applicant's risk assessment is incomplete
   1.1. No explanation has been given for unexpected phenotype changes
   1.2. The application does not include a full molecular characterisation

2. The GM wheat lines contain antibiotic resistance marker genes

3. There is significant potential for damaging escape

4. The proposed trial is unnecessary and will be of no net benefit to society
   4.1. Genetic engineering is neither necessary nor well suited to obtaining elevated micronutrient levels in wheat
   4.2. There is no evidence that the GM wheat will improve nutrition in target groups
   4.3. The planned biofortification may cause harm

1. THE APPLICANT'S RISK ASSESSMENT IS INCOMPLETE

1.1. No explanation has been given for unexpected phenotype changes

As noted in Part A1, paragraph 13 of the application, the applicant's recently concluded (2019 and 2021) UK field trials of biofortified wheat carrying the same *TaVIT2* transcript that features in this application found a 10% decrease in grain size. Separately, Australian trials were conducted in 2015-2017 of GM wheat featuring the *OsNAS2* (nicotianamine synthase 2) gene that has been introduced for this proposed trial. The applicant notes (Part A1, paragraph 16) that "a small but consistent reduction in plant height was observed" in the Australian trials.

Unexpected phenotype changes like these suggest that the genetic engineering has led to unintended changes within the wheat. Such changes could be a result of erroneous genetic alterations, an unexpected impact of the introduced trait/s (eg pleiotropic effects), or an unintended effect of the engineering process itself – all of which could have significant other impacts. However, the application offers no explanation for the unexpected phenotype changes and does not reference any relevant publicly available data. It is irresponsible to allow further experiments to be carried out in an open field without a greater understanding of the cause of these changes.

1.2. The application does not include a full molecular characterisation

In responding to the applicant's 2019 application, 19/R52/02 we highlighted concerns about the absence of a full molecular characterisation[1], noting:

> *It is now widely established that genetic modification is an inherently unpredictable process that is associated with unintended effects at the genetic, epigenetic and cellular level. These unintended effects may go on to have negative agronomic, environmental and health implications, as demonstrated in other GM crop varieties[2,3].*

The use of the vector Agrobacterium tumefaciens has been shown to induce genetic deletions, insertions, chromosomal rearrangements, translocations, scrambling of sequences and epigenetic perturbations[4]. Similarly, the cauliflower mosaic virus 35S promoter has been linked to increased potential for genetic rearrangements[5] and analysis of the nos 3' terminator in transgenic plants has shown that it does not reliably terminate transcription, leading to the generation of novel RNA variants[6]. The applicant does not mention any assessment for genetic rearrangements as observed in other GM varieties[7], or for the absence of novel RNA variants, highlighting a lack of characterisation of the wheat plants.

Once again, the applicant has not performed basic analysis of the introduced DNA or of the integrity of the flanking genomic DNA regions surrounding the transgenic insertions. No wider characterisation of the genome has been performed and no data is presented or cited to confirm the levels of expression of the transgenes.

We note that the Advisory Committee on Releases to the Environment (ACRE)'s advice to Ministers on the applicant's previous application (19/R52/02)[8] stated that molecular characterisations "are not required in applications for small trial releases of GM plants unless they are needed to inform the risk assessment". Given the observed – but unexplained – unexpected phenotype changes (1.1, above); the public funding that supports the research; and the applicant's clear intention to create a viable product for future entry into the food chain, this response is inadequate. The committee is tasked with protecting public health and the natural environment and must surely recognise the importance of identifying potential harms as early as possible in the development of future crops and foodstuff. It should, therefore, demand a full molecular characterisation of the GM plants before considering whether or not to recommend consent for this trial.

2 THE GM WHEAT LINES CONTAIN ANTIBIOTIC RESISTANCE MARKER GENES

Part A1, paragraph 22 of the application states that "The plasmid used possesses two antibiotic resistance genes (nptI and Hyg) and we have assumed that these are integrated into the plant genomic DNA along with the genes of interest. These elements may increase the rates of horizontal gene transfer and establishment in soil bacteria because they provide a theoretical mechanism for homologous recombination and selection (if appropriate antibiotics are present)."

We request that our response to the applicant's 2019 application[9] and previous wheat trials (referenced therein) which also contained the nptI gene is taken into account. Once again, the applicant has not considered the findings by Chinese researchers that synthetic antibiotic-resistance genes were found in microorganisms in Chinese rivers, apparently from plasmids in lab-waste[10].

We note ACRE's view, expressed in the committee's advice on the applicant's previous application for a similar GM wheat field trial(19/R52/01)[11] that UK regulations on the management of laboratory waste make the Chinese research irrelevant. However, we respectfully remind ACRE that our purpose in highlighting this research was – and remains – to highlight the key learning that antibiotic resistance marker genes can persist in environments and be taken up into organisms, even when no selection pressure is applied.

The devastating health, social and economic impacts of the COVID 19 pandemic have highlighted the vulnerability of both human beings and the communities we have created to the spread of infectious disease. The rise of antibiotic resistant infections is recognised as a key concern by the general public, learned organisations such as the European Medicines Agency (EMA)[12] and civil society, where over 500 organisations are represented in the Alliance to Save our Antibiotics[13].

Indeed, in 2019, the UK government published a 20-year vision and 5-year national action plan[14] to prevent further antimicrobial resistance (AMR). The vision calls tackling antimicrobial resistance a "global priority", while the 5-year plan includes the reduction of antimicrobials in agriculture[15]. Agricultural use of antimicrobials is currently restricted to livestock so antibiotic resistance marker genes in GM plants represent a new and additional pathway for pathogenic acquisition of antibiotic resistance. This pathway adds a new threat to the continued efficacy of antibiotics in human and animal medicine.

In this context, it is shocking that the applicant's webpage *FAQs: Planned field trial of high-iron wheat*[16] glosses over the risks of including antibiotic resistance marker genes, stating that "additional pieces of DNA were added to help the insertion of the DNA and to select for plants with the insertion" but without stating that one of the functions of this "additional DNA" is to confer resistance to medically significant antibiotics. This is, at best, disingenuous, given the same page describes other inserted transgenes in some technical detail. The applicant goes on to state that "These extra pieces can be removed later" which begs the question why they have not done so before seeking consent for release into an open field.

Given the possibility of escape (see 3, below), the inclusion of antibiotic marker genes in this trial is irresponsible and the application should be refused.

3 THERE IS SIGNIFICANT POTENTIAL FOR DAMAGING ESCAPE

As we have detailed in previous objections to UK GMO wheat trials[17], wheat has escaped from field trials in the USA on three separate occasions[18] [19]. The discovery of the GM wheat, between eight and 15 years after the conclusion of the GM field trials from which it escaped, prompted some countries to halt purchasing of US wheat[20] and led to market concerns for US farmers and traders. Investigations by APHIS (United States Department of Agriculture – Animal and Plant Health Inspection Service)[21] failed to find the route of contamination in any of these cases.

As we stated in our previous objections:

> "*Together, these incidents present a worrying picture of how easy it is for GM wheat to escape from field trials and remain a GM contamination threat for many years. The uptake and expression of trialled GM traits in other wheat varieties suggests that pollen escaped from the trials. The timelines show that GM wheat trial escapees can remain either undetected or dormant for over 10 years. The impact of these incidents on US wheat trading demonstrates a considerable risk to UK farmers and processors in the event of any escape from the proposed trial.*
>
> *"As the routes of contamination from the US trials are not apparent, it is not possible to suggest mitigation measures that could have prevented the escapes. As a result, open-air field trials of GM wheat should not proceed.*

We note that ACRE, in its advice on a recent GM Wheat field trial application (21/R52/01)[22], dismisses the relevance of the US experience because trials there were more numerous and on a larger scale than each of the individual applications made in the UK. If consent is given, this will be the fifth GM wheat field trial conducted in the UK in recent years, all located in the South and East of England. It will bring the total number of trial seasons for which consent has been given to 16. This trial should not be approved until ACRE has considered the cumulative risk of escape from numerous GM wheat field trials running within relatively close proximity to each other and within the most significant wheat-growing areas of the UK.

4 THE PROPOSED TRIAL IS UNNECESSARY AND WILL BE OF NO NET BENEFIT TO SOCIETY

4.1 Genetic engineering is neither necessary nor well suited to obtaining elevated micronutrient levels in wheat

We detailed in response to the applicant's linked 2019 field trial application (19/R52/02)[23] the evidence suggesting that reduced mineral nutrient levels in wheat is associated with breeding for high yield during the Green Revolution in the last half of the 20th century[24] and that GM approaches are not well suited to solving this problem:

> *"Modern varieties of wheat contain low levels of iron (and zinc), with narrow genetic variation for micronutrient concentrations[25]. In contrast many wild species and traditional varieties (landraces) of wheat contain appreciable levels of iron (and other micronutrients)[26]. This suggests that the current low level of iron in much of the wheat consumed is the result of breeding programmes that have focussed on other factors, such as yield, at the expense of the quality of the resulting grain. Indeed, the loss of mineral nutrients from wheat appears to be associated with breeding for high yield during the Green Revolution in the last half of the 20th century[27].*
>
> *Meanwhile, there is intense research[28] ongoing, using advanced conventional breeding to raise levels of iron and other micronutrients in modern, high yielding varieties of wheat. Hundreds of wild or landrace varieties of wheat have been scanned for genomic markers (regions of DNA) associated with high levels of micronutrients[29]. The identified genomic regions can be incorporated into modern varieties of wheat using methods such as marker assisted selection and genomic selection. These advanced breeding methods rely on conventional breeding processes but track the DNA region of interest to ensure it is present in the offspring[30]. Such advanced conventional breeding methods have already been successful in raising zinc levels in high yielding wheat varieties by 30-40% and there have been promising results for iron[31].*
>
> *The uptake of micronutrients such as zinc and iron tend to be controlled by multiple genes[32]. Such traits are far more suited to advanced conventional breeding methods, which can introduce several genes at once (via conventional breeding), rather than genetic engineering, which tends to focus more on the overexpression of a single gene (for example, the TaVIT2 gene in this application). In addition, it is possible to target the endosperm (the inner wheat grain used for white flour) using such approaches[33]. Hence, conventional breeding approaches are likely to be far more successful in elevating iron levels in wheat than the GM approach employed in this application, without giving rise to food and environmental safety concerns.*

Indeed, the applicant's decision to pursue a new trial when their previous consent (19/R52/02) still has a year to run would suggest that they are experiencing first-hand the limitations of their approach. Unfortunately, adding a second gene – especially where the applicant has failed to provide evidence of efficacy (4.2, below) – is unlikely to make a meaningful difference.

Meanwhile, broader questions have been raised about the impact of industrialised farming practices. For example, an article published in 2020 by Rothamsted Research[34] highlighted the impact of economic factors in the decline of iron and zinc concentrations in modern wheat varieties, acknowledging the proposal that "what we need is a system where farmers should be paid for nutrient yield rather than just mass".

4.2 There is no evidence that the GM wheat will improve nutrition in target groups

The applicant states (Part A1, paragraph 13) that the modifications result in ">2- fold iron in the white flour fraction, increased zinc in white flour and bran fractions, and up to 10-fold more nicotianamine". However, they have not presented any data or referenced any published peer-reviewed literature to confirm this claim and have not provided even their own figures for the claimed increase in zinc content observed in white flour produced from laboratory or greenhouse cultivation of the GM wheat. They have also failed to provide data on the levels of iron in wholewheat or cooked food. As the implied destination for any future end product is industrially produced white bread, such data should include an analysis of nutrient levels following a typical commercial breadmaking process such as the Chorleywood or Activated Dough Development systems.

Similarly, the applicant claims increased bioavailability of the target nutrients as key aim of the project but has not provided any evaluation of the effectiveness of the genetic modifications in in achieving this aim. Part A1, paragraph 15b describes a 5-15-fold increase in expression of the *TaVIT2* transcripts and "highly abundant" *OsNAS2* transcripts but offers no explanation or evidence on how this translates to increased bioavailability of iron and zinc. As with their previous linked trial (19/R52/02) the bioavailability of iron in a cooked, final product remains unknown[35].

The comments we made in response to the applicant's linked 2019 field trial application (19/R52/02)[36] regarding the wider implications of improving the micronutrient profile of white flour apply equally to this proposed field trial:

> *"This project focuses on increasing iron* [and zinc] *in the endosperm but the promotion of white flour to tackle iron* [and/or zinc] *deficiency would undermine community understanding and acceptance of core health messages. Rather than creating iron-rich white sliced bread and doughnuts, efforts should focus on continued promotion of the importance of consuming wholegrains as well as research to understand barriers to maintaining a healthy diet. Consuming a varied diet that combines micronutrients with fibre, protein and a healthy balance of complex carbohydrates and fats is key to good health as it not only achieves optimum nutrition but also supports a healthy gut microbiome[37]."*

Published NHS advice states that "You should be able to get all the zinc you need by eating a varied and balanced diet" [38] and, similarly, that "You should be able to get all the iron you need from your daily diet"[39]. A key barrier to achieving good nutrition is not just the widespread use of refined white flour but also the "no time" fermentation systems (for example the Chorleywood Breadmaking Process) favoured in industrial food production. Fermentation, especially with sourdough microorganisms, allows for the natural breakdown of phytate, reducing its chelating effect to increase iron bioavailability[40] as well as improving digestibility and contributing to a healthy gut microbiome. Rather than manipulating the genome of a staple crop in the hope of achieving a marginal improvement in the nutritional content of industrial white bread, the applicants – and the public funding they receive – would be better focused on addressing the systemic problems that prevent the widespread availability and consumption of "real" bread.

Considering the potential distribution of the proposed future GM crop in the global south, we highlight further comments we made in response to the applicant's linked 2019 field trial application (19/R52/02)[41]:

> *"It is also important to consider that iron requirements differ between populations[42]. Employing GM crops to address global iron deficiency is arguably a reductionist and simplistic approach to a problem that should be tackled holistically. Addressing micronutrient deficiency by identifying barriers to a culturally relevant healthy diet and gaining a deeper understanding of local needs will bring significantly broader and more long-lasting benefits than introducing a GM biofortified crop."*

4.3 The planned biofortification may cause harm

As noted in our response to the applicant's linked 2019 field trial application (19/R52/02)[43], biofortification carries significant risks, particularly when applied to a staple foodstuff such as wheat.

> *Toxic elements including cadmium and lead enter plant cells largely via the same pathways that are responsible for the uptake of essential metals such as iron. It is appropriate, therefore, to be concerned about the possibility that biofortification by genetic modification could lead to increased levels of toxic heavy metals and associated adverse health effects.*

Despite their own study observing a significant increase in cadmium in lines that contained over 20 copies of the transgene[44], the applicant has not provided any data on levels of toxic elements present in the wheat grown in that trial (19/R52/02) or this new crop. They also make no indication that this issue, which is vital to the safety and viability of any future crop developed as a result of the proposed trial, will be assessed as part of this experimental programme.

Similarly, the applicant demonstrates no understanding of the harm caused by excessive iron uptake, which can lead to abdominal problems, nausea and intestinal damage. Sufferers of haemochromatosis - a hereditary condition, which the NHS notes as being particularly common in Ireland, Scotland and Wales[45] - are particularly vulnerable. There is currently no cure for haemochromatosis which causes damage to the liver, joints, pancreas and heart through the build-up of iron. Published NHS guidance states that patients with this condition will "usually be advised to avoid breakfast cereals containing added iron"[46] so it can be assumed that they would also need to avoid biofortified wheat products.

As the applicant has not provided meaningful data on the bioavailability of either iron or zinc in finished food products made from the GM plants included in the proposed trial, it is not possible to predict whether their release – through accidental escape from this trial, or future roll-out of a commercial crop based on these experiments – will contribute to addressing nutrient deficiency or lead to excessive uptake, particularly in vulnerable groups. The trial should not proceed until such data has been gathered through contained use studies.

The proposed trial represents an unacceptable risk to our farms and our food. Any future cultivation of the crops in the proposed trial is unlikely to achieve the desired improvements in nutrition and risks causing significant harm. We request, therefore, that the Minister denies consent and prevents this open-air field trial going ahead.

Yours faithfully

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References

[1] GM Freeze et al. 2019. Defra: Multi-agency response to GM wheat trial 19/R52/02. https://www.gmfreeze.org/wp-content/uploads/2019/02/Multi-agency-response-to-GM-wheat-trial-application-19_R52_02-.pdf

[2] Mesnage, R., Agapito-Tenfen, S.Z., Vilperte, V., Renney, G., Ward, M., Séralini, G.E., Nodari, R.O. & Antoniou, M.N. 2016. An integrated multi-omics analysis of the NK603 Roundup-tolerant GM maize reveals metabolism disturbances caused by the transformation process. Scientific Reports 19: 37855.

[3] Bollinedi, H., S, G.K., Prabhu, K.V., Singh, N.K., Mishra, S., Khurana, J.P. & Singh, A.K. 2017. Molecular and functional characterization of GR2-R1 event based backcross derived lines of golden rice in the genetic background of a mega rice variety Swarna. PLoS One 12: e0169600.

[4] Jupe, F., Rivkin, A.C., Michael, T.P., Zander, M., Motley, S.T., Sandoval, J.P., Slotkin, R.K., Chen, H., Castanon, R., Nery, J.R. & Ecker, J.R. 2019. The complex architecture and epigenomic impact of plant T-DNA insertions. PLoS Genetics 15: e1007819..

[5] Ho, M.W., Ryan, A. & Cummins, J. 1999. Cauliflower mosaic viral promoter – a recipe for disaster? Microbial Health and Disease. 11: 194–197.

[6] EFSA 2009. Scientific Opinion of the Panel on Genetically Modified Organisms on applications (EFSA-GMO-NL-2005-22 and EFSA-GMO-RX-NK603) for the placing on the market of the genetically modified glyphosate tolerant maize NK603 for cultivation, food and feed uses and import and processing, and for renewal of the authorisation of maize NK603 as existing product. The EFSA Journal 1137: 1-50.

[7] Ho MW. 2008. Transgenic lines unstable hence illegal and ineligible for protection. Science in Society 38: 28-29.

[8] ACRE 2019. Advice: application for a trial of GM wheat (19/R52/02) https://www.gov.uk/government/publications/acre-advice-application-for-a-trial-of-gm-wheat-19r5202

[9] GM Freeze et al. 2019. Defra: Multi-agency response to GM wheat trial 19/R52/02. https://www.gmfreeze.org/wp-content/uploads/2019/02/Multi-agency-response-to-GM-wheat-trial-application-19_R52_02-.pdf

[10] Chen, J., Jin, M., Qiu, Z-G., Guo, C., Chen, Z-L., Shen, Z-Q., Wang, X-W. & Li, J-W. 2012. A survey of drug resistance *bla* genes originating from synthetic plasmid vectors in six Chinese rivers. Environmental Science and Technology 46: 13448-13454.
[11] ACRE. 2019. Advice: application for a trial of GM wheat (19/52/02) https://www.gov.uk/government/publications/acre-advice-application-for-a-trial-of-gm-wheat-19r5202
[12] See, e.g. EMA 2018. Antimicrobial resistance. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/antimicrobial-resistance
[13] https://www.saveourantibiotics.org/alliance-members/
[14] UK Department for Environment, Food & Rural Affairs, Department of Health and Social Care, Public Health England, and Veterinary Medicines Directorate 2019. Antimicrobial resistance (AMR). Policy papers 24th January https://www.gov.uk/government/collections/antimicrobial-resistance-amr-information-and-resources
[15] UK Department of Health and Social Care 2019. Tackling antimicrobial resistance 2019–2024 The UK's five-year national action plan https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/773130/uk-amr-5-year-national-action-plan.pdf
[16] https://www.jic.ac.uk/research-impact/planned-field-trial-of-high-iron-wheat/
[17] GM Freeze et al. 2016. Defra: Multi-agency response to wheat trial 16/R8/02. https://www.gmfreeze.org/wp-content/uploads/2017/04/Multi_agency_response_to_GM_wheat_trial_application_16_R8_02.pdf
GM Freeze et al. 2019. Defra: Multi-agency response to wheat trail 19/R5/02. https://www.gmfreeze.org/wp-content/uploads/2019/02/Multi-agency-response-to-GM-wheat-trial-application-19_R52_02-.pdf
GM Freeze et al. 2021. Defra: Multi-agency response to GM wheat trial 21/R08/01 https://www.gmfreeze.org/wp-content/uploads/2021/06/Multi-agency-response-to-GM-wheat-trial-application-ref-21_R08_01-UPDATED.pdf
[18] USDA APHIS 2014a. USDA announces close and findings of investigation into the detection of genetically engineered wheat in Oregon in 2013. https://www.aphis.usda.gov/newsroom/2014/09/pdf/ge_wheat.pdf
USDA APHIS 2014b. Questions and answers: genetically engineered wheat investigation. September 2014. https://www.aphis.usda.gov/publications/biotechnology/2014/faq_ge_wheat.pdf;
[19] USDA APHIS 2016. December 1, 2016 Update regarding detection of GE wheat volunteer plants in Washington state (incorporating August 5, 2016 and July 29, 2016 Statements on detection of GE wheat volunteer plants in Washington state) https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/brs-news-and-information/2016_brs_news/wheat_fact_finding_closed
[20] Fox, J.L. 2013. Volunteer GM wheat, mischief or carelessness? Nature Biotechnology 31: 669-670.
[21] USDA APHIS 2014a. USDA announces close and findings of investigation into the detection of genetically engineered wheat in Oregon in 2013. https://www.aphis.usda.gov/newsroom/2014/09/pdf/ge_wheat.pdf
USDA APHIS 2014b. Questions and answers: genetically engineered wheat investigation. September 2014. https://www.aphis.usda.gov/publications/biotechnology/2014/faq_ge_wheat.pdf
and USDA APHIS 2016. December 1, 2016 Update regarding detection of GE wheat volunteer plants in Washington state (incorporating August 5, 2016 and July 29, 2016 Statements on detection of GE wheat volunteer plants in Washington state) https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/brs-news-and-information/2016_brs_news/wheat_fact_finding_closed
[22] ACRE 2021. ACRE advice on application on an application for deliberate release of a GMO for research and development purposes, ref 21/R08/01 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1018887/Advice_on_an_application_for_deliberate_release_of_a_GMO_for_research_and_development_purposes.pdf
[23] GM Freeze et al. 2019. Defra: Multi-agency response to GM wheat trial 19/R52/02. https://www.gmfreeze.org/wp-content/uploads/2019/02/Multi-agency-response-to-GM-wheat-trial-application-19_R52_02-.pdf
[24] Fan, M.S., Zhao, F.J., Fairweather-Tait, S.J., Poulton, P.R., Dunham, S.J. & McGrath, S.P. 2008. Evidence of decreasing mineral density in wheat grain over the last 160 years. Journal of Trace Elements in Medicine and Biology 22: 315–324.
[25] Velu, G., Tutus, Y, Gomez-Becerra, H.F. et al. 2017. QTL mapping for grain zinc and iron concentrations and zinc efficiency in a tetraploid and hexaploid wheat mapping populations. Plant and Soil 411: 81–99.
[26] Manickavelu, A., Hattori, T., Yamaoka, S., Yoshimura, K., Kondou, Y., Onogi, A., Matsui, M., Iwata, H. & Ban, T. 2017. Genetic nature of elemental contents in wheat grains and its genomic prediction: toward the effective use of wheat landraces from Afghanistan. PLoS ONE 12: e0169416.; Velu, G., Crossa, J., Singh, R.P et al. 2016. Genomic prediction for grain zinc and iron concentrations in spring wheat. Theoretical and Applied Genetics 129: 1595–1605; Kumar, U., Mathpal, P., Malik, S. & Kumar, N. 2016. Evaluation of iron and zinc in grain and grain fractions of hexaploid wheat and its related species for possible utilization in wheat biofortification. Plant Genetic Resources 14: 101-111.
[27] Fan, M.S., Zhao, F.J., Fairweather-Tait, S.J., Poulton, P.R., Dunham, S.J. & McGrath, S.P. 2008. Evidence of decreasing mineral density in wheat grain over the last 160 years. Journal of Trace Elements in Medicine and Biology 22: 315–324.
[28] See, e.g. Velu, G., Singh, R.P. & Crespo-Herrera, L. 2018. Genetic dissection of grain zinc concentration in spring wheat for mainstreaming biofortification in CIMMYT wheat breeding. Nature Scientific Reports 8: 13526.; Velu, G.,

Tutus, Y, Gomez-Becerra, H.F. et al. 2017. QTL mapping for grain zinc and iron concentrations and zinc efficiency in a tetraploid and hexaploid wheat mapping populations. Plant and Soil 411: 81–99; Velu, G., Crossa, J., Singh, R.P et al. 2016. Genomic prediction for grain zinc and iron concentrations in spring wheat. Theoretical and Applied Genetics 129: 1595–1605.
[29] Manickavelu, A., Hattori, T., Yamaoka, S., Yoshimura, K., Kondou, Y., Onogi, A., Matsui, M., Iwata, H. & Ban, T. 2017. Genetic nature of elemental contents in wheat grains and its genomic prediction: toward the effective use of wheat landraces from Afghanistan. PLoS ONE 12: e0169416.; Velu, G., Crossa, J., Singh, R.P et al. 2016. Genomic prediction for grain zinc and iron concentrations in spring wheat. Theoretical and Applied Genetics 129: 1595–1605.
[30] See, e.g. Bevan, M.W., Uauy, C., Wulff, B.B.H., Zhou, J., Krasileva, K. & Clark, M.D. 2017. Genomic innovation for crop improvement. Nature 543: 346–354.
[31] Velu, G., Singh, R.P., Crespo-Herrera, L. 2018. Genetic dissection of grain zinc concentration in spring wheat for mainstreaming biofortification in CIMMYT wheat breeding. Nature Scientific Reports 8: 13526.
[32] Velu, G., Singh, R.P., Crespo-Herrera, L. 2018. Genetic dissection of grain zinc concentration in spring wheat for mainstreaming biofortification in CIMMYT wheat breeding. Nature Scientific Reports 8: 13526.z
[33] Kumar, U., Mathpal, P., Malik, S. & Kumar, N. 2016. Evaluation of iron and zinc in grain and grain fractions of hexaploid wheat and its related species for possible utilization in wheat biofortification. Plant Genetic Resources 14: 101-111.
[34] McGrath, S., Shewry P. 2020. Fact or fake News: is our food becoming less nutritious? https://www.rothamsted.ac.uk/articles/fact-or-fake-news-our-food-becoming-less-nutritious
[35] Connorton, J.M., Jones, E.R., Rodríguez-Ramiro, I., Fairweather-Tait, S., Uauy, C. & Balk, J. 2017. Wheat vacuolar iron transporter TaVIT2 transports Fe and Mn and is effective for biofortification. Plant Physiology 174: 2434-2444.
[36] GM Freeze et al. 2019. Defra: Multi-agency response to GM wheat trial 19/R52/02. https://www.gmfreeze.org/wp-content/uploads/2019/02/Multi-agency-response-to-GM-wheat-trial-application-19_R52_02-.pdf
[37] For reviews, see Valdes, A.M., Walter, J., Segal, E. & Spector, T.D. 2018. Role of the gut microbiota in nutrition and health. The BMJ 361: k2179; Kau, A.L., Ahern, P.P., Griffin, N.W., Goodman, A.L. & Gordon, J.I. 2011. Human nutrition, the gut microbiome and the immune system. Nature 474: 327–336.
[38] NHS 2021. Health A-Z, Vitamins and minerals – others https://www.nhs.uk/conditions/vitamins-and-minerals/others/
[39] NHS 2021. Health A-Z, Vitamins and minerals – Iron https://www.nhs.uk/conditions/vitamins-and-minerals/iron/
[40] Rodrquez-Ramiro L, Brearley CA, Bruggraber SFA, Perfecto A, Shewry P, Fairweather-Tait S, 2017, Assessment of iron bioavailability from different bread making processes unsing an *in vitro* intestinal cell model. Food Chemistry. 228:91-98. Doi: 10.1016/j.foodchem.2017.01.130
[41] GM Freeze et al. 2019. Defra: Multi-agency response to GM wheat trial 19/R52/02. https://www.gmfreeze.org/wp-content/uploads/2019/02/Multi-agency-response-to-GM-wheat-trial-application-19_R52_02-.pdf
[42] Schümann, K., Ettle, T., Szegner, B., Elsenhans, B. & Solomons, N.W. 2007. On risks and benefits of iron supplementation recommendations for iron intake revisited. Journal of Trace Elements in Medicine and Biology 21: 147-68.
[43] GM Freeze et al. 2019. Defra: Multi-agency response to GM wheat trial 19/R52/02. https://www.gmfreeze.org/wp-content/uploads/2019/02/Multi-agency-response-to-GM-wheat-trial-application-19_R52_02-.pdf
[44] Connorton JM, Jones ER, Rodríguez-Ramiro I, Fairweather-Tait S, Uauy C, Balk J. 2017. Wheat Vacuolar Iron Transporter TaVIT2 Transports Fe and Mn and Is Effective for Biofortification. Plant Physiology. 174(4):2434-2444. doi: 10.1104/pp.17.00672
[45] NHS 2021. Health A-Z. Haemochromatosis https://www.nhs.uk/conditions/haemochromatosis/
[46] NHS 2021. Health A-Z. Haemochromatosis https://www.nhs.uk/conditions/haemochromatosis/