FAQ on Genome Editing and CRISPR/Cas9

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Genome editing is a generic term for new methods enabling targeted modifications to the genetic material (genome) of a cell. The CRISPR/Cas9 method in particular holds great promise for new application methods. The German Federal Institute for Risk Assessment (BfR) systematically monitors these developments in the interest of consumer health protection. In this FAQ, the BfR answers the most important questions on the topic of genome editing and the CRISPR/Cas9 method in particular.

In November 2016, the Federal Government issued a statement entitled “Classification and management of new genetic engineering techniques”.
http://dip21.bundestag.de/dip21/btd/18/103/1810301.pdf (in German)

A group of scientific advisors from the European Commission published an assessment of new techniques in agricultural biotechnology in April 2017.
http://ec.europa.eu/research/sam/pdf/topics/explanatory_note_new_techniques_agricultural_biotechnology.pdf

The legal status of genome editing as a genetic engineering technique was clarified in a ruling from the European Court of Justice (ECJ) in July 2018:
http://curia.europa.eu/juris/liste.jsf?language=en&td=ALL&num=C-528/16

Approaches to the detection of food and feed plant products obtained by new mutagenesis techniques have been analysed by the European Network of GMO Laboratories (ENGL).
http://gmo-crl.jrc.ec.europa.eu/doc/JRC116289-GE-report-ENGL.pdf

What is genome editing?

Genome editing means the deliberate editing of genetic information. It is an umbrella term used to denote a range of new methods in molecular biology that enables targeted modifications to be made to genetic information.

Genome editing techniques can be used to induce specific changes in the genome of the target organism. To do so, two components are required: a protein (nuclease) that "cuts" the DNA of the target organism and a "guide" that steers this nuclease to the relevant position in the DNA. As part of the process, the "guide" (a piece of DNA, RNA or a protein, depending on the technique used) is customised in such a way that it can identify the relevant location in the genome of the target organism. The nuclease can be introduced into the cell either externally (CRISPR/Cas9, TALEN, zinc finger nuclease) or it can be naturally contained within the cell itself (ODM).

These procedures can result in a point mutation (replacement of a single DNA building block, known as a nucleotide) or a deletion (elimination of one or more nucleotides). One or more nucleotides can also be added (known as insertion). Scientists can even introduce a larger piece of synthetic DNA into the cell, which is then integrated into the genome during DNA repair.

How do genome editing and conventional plant breeding methods differ, and what are their common features?
Conventional plant breeding (i.e. not using genetic engineering) uses a plant's natural affinity for cross-breeding as well as changes introduced into the plant genome either randomly, or triggered by chemicals or irradiation. Breeders do not know exactly where in the genome these changes occur. In a subsequent selection process, the treated cells or plant clones are examined in order to identify and select those of them that exhibit the desired modification(s). These techniques have already been used successfully over 3,000 times for the cultivation of new plant varieties. Certain barley varieties, for example, were produced with the help of gamma rays.

In contrast, genome editing induces targeted modifications in genes. What form the modification takes at the defined location depends on how the tools are used as part of the genome editing process (see above). In some cases, the final result (DNA sequence) offers no clues as to whether a mutation has taken place naturally or as a result of a new scientific technique. However, by introducing DNA derived from other species, genome editing can also create genetic variants that would never occur in nature.

Does making changes to genetic information automatically pose a health risk?
Minor modifications in the genome are common to all life on earth. Every time a cell divides, DNA has to be copied (replicated) to ensure that all daughter cells have a full set of genetic information. Minor errors occur repeatedly in this process. Individual nucleotides may become altered and shorter or longer sequences can be lost entirely. In humans, the number of uncorrected replication errors is estimated to be 1 in 10^9 to 10^{11} replicated (copied) nucleotides. These errors cause visible changes in the organism (to its phenotype) only very rarely. Accordingly, making changes to a sequence of DNA does not automatically create a health concern. However, the risk assessment process also investigates whether a genetic sequence modified by genome editing has been altered in a way that gives the organism new properties.

In the EU, there is a set of established procedures and guidelines for conducting risk assessments of this kind, which enables an examination on the basis of available scientific information and data in accordance with the applicable national and local legislation.

What does the CRISPR/Cas9 acronym mean?
CRISPR stands for **C**lustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats. These are repeated DNA sequences that occur in the genomes of many bacteria and which play an important role in bacterial defence systems. When a virus enters a bacterium, the bacterial cell incorporates parts of the viral DNA into its own CRISPR structure. If another virus with this DNA enters the bacterium, it will be recognised by these same CRISPR sequences. Cas9 is the abbreviation for ***C**RISPR-**as**sociated protein **9***. The Cas9 enzyme latches onto a recognised sequence of DNA and cuts viral DNA (acting as a nuclease). This inactivates the virus.

How does CRISPR/Cas9 work?
CRISPR and Cas9 were originally discovered as part of a system that protects bacteria from the introduction of foreign genetic material (extrachromosomal DNA) by viruses or plasmids. For a few years now, CRISPR/Cas9 has been used and further developed as part of a specific genome editing technique: a piece of "guide" RNA is attached to the Cas9 enzyme – this guide RNA then assumes the role of the viral DNA, i.e. the detection mechanism. When Cas9 finds the matching piece of genomic DNA, it cuts the DNA double strand. This DNA

break can subsequently be repaired in a number of different ways by cell-specific processes, which can result in mutations (see above).

What are the application areas for genome editing?
Genome editing is a comparatively simple laboratory technique, and is also quicker and much more precise than previously applied methods (including conventional genetic engineering methods). Accordingly, scientists hope that genome editing can help plant breeding and animal husbandry to achieve higher-yield or more disease-resistant varieties and breeds, such as mildew-resistant wheat and potatoes that can tolerate cool storage conditions. In the field of medicine, researchers expect to see genome editing provide a fresh impetus for developing novel therapeutic procedures for a range of diseases.

How can genome editing be detected?
Where larger portions of foreign DNA have been introduced into an organism by genetic techniques (either conventional genetic engineering or certain kinds of genome editing), this organism is usually easily detectable as a genetically-modified organism (GMO) as defined by the EU GMO Directive. Nevertheless, there is always a danger that something unfamiliar will not be properly detected.

Importantly, the detection of altered DNA is not necessarily the prove of a specific technique used, in cases where a number of different approaches would produce an identical result (natural methods or conventional mutagenesis techniques – see above section, “How do genome editing and conventional plant breeding methods differ, and what are their common features?”).

Taking point mutation as an example (see section, “What is genome editing?”), it is currently impossible to distinguish here between the results of genome editing and the effects of changes introduced by other methods or factors (natural mutation, conventional mutagenesis techniques).

European legislation also provides the possibility for a set of end-to-end documentation as part of ensuring the traceability of GMOs that have been created with the help of genome editing.

How is it possible to assess the potential health risks posed to consumers by genome editing in the area of food and feed safety?
It is a basic principle enshrined in EU law that unsafe food and feed must not be placed on the market.

On the view of the expert group at the EU Commission, case-by-case assessment is necessary in order to evaluate the risk posed by organisms created by new techniques (i.e. genome editing).

In principle, established procedures used in the risk assessment of food and feed derived from genetically modified plants can also be applied to the risk assessment of plants that have been created by means of genome editing.

The starting point for GMO risk assessment is to compare the GMO with a suitable reference organism (for genetically-modified maize, this would be the original unmodified maize line), which involves analyzing the molecular structures, the most important constituents, the allergenic potential, the toxicological and nutritional properties, and environmental safety aspects. Internationally agreed guidelines are then applied to review and assess any differences detected on a case-by-case basis in order to identifiy potential health concerns. This same procedure can also be applied to organisms created by using genome editing techniques.

Is genome editing a genetic engineering method?
On 25 July 2018, the European Court of Justice (ECJ) ruled as follows: organisms created by genome editing are genetically modified organisms (GMOs) as defined by the GMO Directive of the European Parliament and of the European Council, and are therefore subject to genetic engineering regulations.

From the ECJ ruling it also follows that products manufactured in this manner must be subject to the labelling requirements for genetically modified organisms, so that they can be properly identified as such by consumers.

What is the BfR's remit in the field of genome editing?
The institute's work focuses primarily on the protection of human health. Through its independent scientific assessments, research and clear-cut communication of health risks, the BfR makes an impartial contribution to the safety of food and feed, products and chemicals. Against this background, the BfR also engages with genome editing as a field of scientific research, and as such is involved in regular dialogue with national, European and other international institutions.

As a scientific institution responsible for the risk assessment, the BfR is not in charge of the classification of genome editing from a legal perspective. In accordance with its remit, the BfR works with other German government agencies to assess not the technique of genome editing itself but the food and feed products that it is used to modify. The risk assessment here is conducted on the basis of the method used to make these products. Applicants must also submit information about the genetic changes that have been introduced into the genome by the technique as applied.

On 6 December 2016, the BfR held a symposium entitled 'New Technologies for the Modification of the Genome' to provide up-to-date knowledge of the subject and offer a platform to discuss its various topics. In hosting this inaugural event, the BfR acted in line with its legal mandate to communicate potential, identified and assessed risks in a balanced and scientifically sound manner.

The BfR will organise a consumer congress on genome editing in autumn 2019. This event is intended to promote informed and nuanced consumer opinion about the application of genome editing, and will culminate in the holding of a 'consumer vote'. The result of this vote will be formally presented to representatives from politics, research, business and civil society in a final conference..

What role is played by the BfR Committee for Genetically Modified Food and Feed?
The members of BfR committees are volunteers who provide independent advice on unresolved issues in science and research. The BfR committees are not involved in the BfR's risk assessment work.

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. It advises the Federal Government and Federal Laender on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.

This text version is a translation of the original German text which is the only legally binding version.