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. In particular, possible applications of CRISPR/Cas9 are already described in a large number of publications. 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. This term encompasses various new molecular-biological methods, which can be used to modify genetic information in a targeted manner.

With the methods of genome editing, targeted changes can be introduced in the genome of the target organism. Two components are required for this: 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 either be introduced into the cell from outside (these techniques are called CRISPR/Cas9, TALEN, zinc finger nuclease) or be naturally present in the cell (OGM).

A point mutation (exchange of a single DNA building block, the so-called nucleotides) or a deletion (omission of a single nucleotide or several nucleotides) can occur. One or more nucleotides can also be added (insertion). Scientists can even introduce a larger piece of synthetic or foreign 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?

In conventional plant breeding (non-genetic engineering methods), in addition to the natural crossing of plants, spontaneous or chemical or radiation-induced changes in the plant genome are also used, which lead to changes at various random locations in the genome. 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, it is not possible to determine on the basis of the result (DNA sequence) whether a mutation has taken place naturally or through a new technique. With the help of genome editing, however, genetic variants can also be created that do not arise naturally (introduction of foreign DNA).

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). Scientists therefore hope that with the help of genome editing in plant and animal breeding, higher-yielding or disease-resistant varieties and breeds will emerge, e.g. mildew-resistant wheat or potatoes that can be stored under cool conditions. In the field of medicine, research is being carried out into how genome editing can spur on the development of new therapy methods for various diseases.

How can genome editing be detected?

An organism into which larger elements of foreign DNA have been introduced with the help of certain variants of genome editing or with the help of classic genetic engineering can usually be easily identified as a genetically modified organism (GMO) within the meaning of the GMO Directive. Numerous detection methods for various GMOs have already been developed and are available to the food and animal feed testing authorities for monitoring. Nevertheless, there is always a danger that something unfamiliar will not be detected.

Important: The detection of altered DNA is not necessarily the same as the detection of a specific method, provided that the same result could have been achieved in different ways (of course, classic mutagenesis methods; see question "What are the differences and similarities between genome editing and conventional methods of plant breeding?").

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).

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, the established procedures for the health risk assessment of food and animal feed from genetically modified plants can also be applied to the risk assessment of plants that were generated with the help 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 analysing 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 identify potential health concerns. This principle of "substantial equivalence" can also be applied to organisms created with the help of genome editing.

Is genome editing a genetic engineering method?

As a scientific institution, the BfR has no opinion on the classification of genome editing from a legal perspective. 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.

It also follows from the ECJ ruling that products manufactured in this way are subject to the obligation to label GMOs and must therefore be identified for 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 organised a consumer conference on genome editing in autumn 2019. The conference promoted variegation of opinion among informed consumers on the use of genome editing via a consumer vote. This consumer vote (https://www.bfr.bund.de/cm/349/consumer-vote-genome-editing.pdf) was submitted to representatives from politics, science, business and civil society at the final conference.

In March 2023, the BfR, together with the Julius Kühn Institute (JKI), and the Federal Office of Consumer Protection and Food Safety (BVL) and the Joint Research Center of the European Commission (EC-JRC), will hold a conference entitled "International Conference on GMO Analysis and New Genomic Techniques" (https://www.bfr-akademie.de/gmo2023/). In addition to the basic topics of GMO detection, a special focus should be placed on genome editing and its detectability. The results of the conference can be added to the considerations of the European Commission on the new regulation of genome editing.

What role is played by the BfR Committee for Genetically Modified Food and Feed?

The Commission for Genetically Modified Food and Animal Feed advises the BfR as a voluntary and independent expert body on questions of food and animal feed safety of products made from genetically modified organisms. As an instrument of external quality assurance, the commission increases the scientific quality of the BfR's statements and can support the institute in an advisory capacity as an expert network in the event of a crisis. The Commission consists of eleven members who have been appointed for a four-year cycle through an open call for applications and are distinguished by their scientific expertise in their respective fields. The members of the Commission are bound to secrecy towards third parties and to fulfil their task impartially. Any conflicts of interest on individual agenda items dealt with in the meeting are requested and disclosed in a transparent manner. The scientific opinion of the BfR Commission is based in part on the results protocols that are made available. The Commission's recommendations are purely advisory in nature. The Commission itself does not issue any rulings or reports and is not authorised to give instructions to the BfR (and vice-versa) and is not involved in its risk assessments. Further information on the BfR Commission can be found here.

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the German Federal Ministry of Food and Agriculture (BMEL). The BfR advises the Federal Government and the States (‘Laender’) on questions of food, chemicals and product safety. The BfR conducts independent 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.