

Cancer Association of South Africa (CANSA)



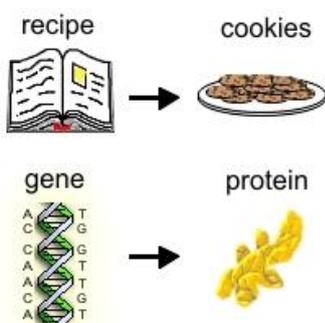
Fact Sheet on Genetic Engineering

Introduction

Genetic engineering is the process of manually adding new deoxyribonucleic acid (DNA) to an organism. The goal is to add one or more new traits that are not already found in that organism. Examples of genetically engineered (transgenic) organisms currently on the market include plants with resistance to some insects (cotton), plants that can tolerate herbicides (maize), and crops with modified oil content (soy bean).



[Picture Credit: GMO]



DNA is the recipe for life. DNA is a molecule found in the nucleus of every cell and is made up of 4 subunits represented by the letters A (Adenine), T (Thymine), G (Guanine), and C (Cytosine). The order of these subunits in the DNA strand holds a code of information for the cell. Just like the English alphabet makes up words using 26 letters, the genetic language uses 4 letters to spell out the instructions for how to make the proteins an organism will need to live and grow.

Small segments of DNA are called genes. Each gene holds the instructions for how to produce a single protein. This can be compared to a recipe for making a food dish. A recipe is a set of instructions for making a single dish.

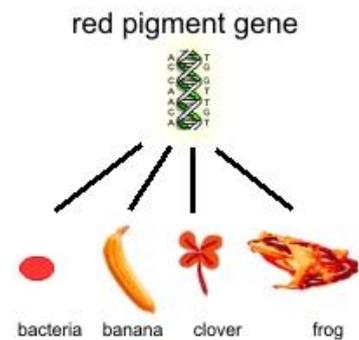
An organism may have thousands of genes. The set of all genes in an organism is called a genome. A genome can be compared to a cookbook of recipes that makes that organism what it is. Every cell of every living organism has a 'cookbook'.

Proteins do the work in cells. They can be part of structures (such as the cell walls, organelles, etc). They can regulate reactions that take place in the cell or they can serve as enzymes, which speed up reactions. Everything one sees in an organism is either made of proteins or the result of a protein reaction.

DNA is a 'universal language', meaning the genetic code means the same thing in all organisms. It would be like if all cookbooks around the world were written in a single language that everyone knew. This characteristic is critical to the success of genetic engineering. When a gene for a desirable trait is

taken from one organism and inserted into another, it gives the 'recipient' organism the ability to express that exact same trait.

Genetic engineering, also called 'genetic transformation', 'genetic enhancement' or 'genetic modification', works by physically removing a gene from one organism and inserting it into another, giving it the ability to express the trait encoded by that gene. It is like taking a single recipe out of a cookbook and placing it into another cookbook.



Hirschi, K.D. 2020.

"Combating malnutrition is one of the greatest global health challenges. Plant-based foods offer an assortment of nutrients that are essential for adequate nutrition and can promote good health. Unfortunately, the majority of widely consumed crops are deficient in some of these nutrients. Biofortification is the umbrella term for the process by which the nutritional quality of food crops is enhanced. Traditional agricultural breeding approaches for biofortification are time consuming but can enhance the nutritional value of some foods; however, advances in molecular biology are rapidly being exploited to biofortify various crops. Globally, genetically modified organisms are a controversial topic for consumers and governmental agencies, with a vast majority of people apprehensive about the technology. Golden Rice has been genetically modified to contain elevated β -carotene concentrations and is the bellwether for both the promise and angst of agricultural biotechnology. Although there are numerous other nutritional targets of genetically biofortified crops, here I briefly summarize the work to elevate iron and folate concentrations. In addition, the possibility of using modified foods to affect the gut microbiota is examined. For several decades, plant biotechnology has measured changes in nutrient concentrations; however, the bioavailability of nutrients from many biofortified crops has not been demonstrated."

The Process of Genetic Engineering

Once a goal is in mind ...

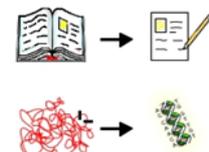
1. One needs to find an organism that naturally contains the desired trait.



2. The DNA is then extracted from the particular organism. This is like taking out the entire cookbook.



3. The one desired gene (a single recipe) must be located and copied from the thousands of genes that were extracted. This is called gene cloning.



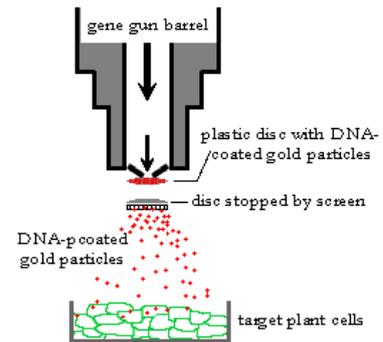
4. The gene may be modified slightly to work in a more desirable way once inside the recipient organism.

5.

The new gene(s), called a transgene, is delivered into cells of the recipient organism. This is called transformation. The most common



transformation technique uses a bacteria that naturally genetically engineer plants with its own DNA. The transgene is inserted into the bacteria, which then delivers it into cells of the organism being engineered. Another technique, called the gene gun method (see picture on the left), shoots microscopic gold particles coated with copies of the transgene into cells of the recipient organism (picture right).



With either technique, genetic engineers have no control over where or if the transgene inserts into the genome. As a result, it takes hundreds of attempts to achieve

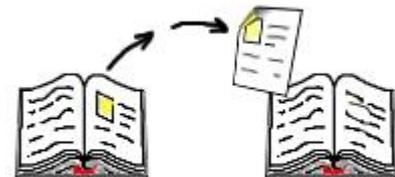
just a few transgenic organisms (Gene Gun; Shooting Gene Gun).

6.

Once a transgenic organism has been created, traditional breeding is used to improve the characteristics of the final product. Genetic engineering does not eliminate the need for traditional breeding. It is simply a way to add new traits to the pool.

Although the goal of both genetic engineering and traditional plant breeding is to improve an organism's traits, there are some key differences between them.

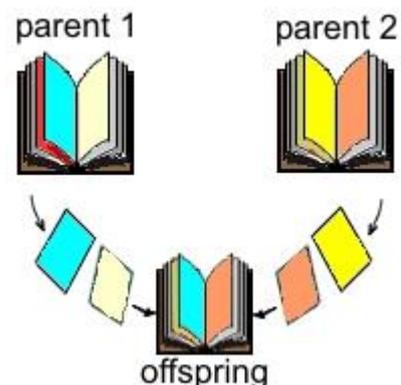
genetic engineering



While genetic engineering manually moves genes from one organism to another, traditional breeding moves genes through mating, or crossing, the organisms in hopes of obtaining offspring with the desired combination of traits.

Using the recipe analogy, traditional breeding is like taking two cookbooks and combining every other recipe from each into one cookbook. The product is a new cookbook with half of the recipes from each original book. Therefore, half of the genes in the offspring of a cross come from each parent.

traditional breeding



Traditional breeding is effective in improving traits, however, when compared with genetic engineering, it does have disadvantages. Since breeding relies on the ability to mate two organisms to move genes, trait improvement is basically limited to those traits that already exist within that species. Genetic engineering, on the other hand, physically removes the genes from one organism and places them into the other. This eliminates the need for mating and allows the movement of genes between organisms of any

species. Therefore, the potential traits that can be used are virtually unlimited.

Breeding is also less precise than genetic engineering. In breeding, half of the genes from each parent are passed on to the offspring. This may include many undesirable genes for traits that are not wanted in the new organism. Genetic engineering, however, allows for the movement of a single, or a few, genes.

The Steps in Conducting Genetic Engineering

Behind every single seed is at least a decade of research involving geneticists, engineers and farmers, working to produce a seed that will grow exactly as expected, and in a way nature may not have intended.

Step one: Finding a new trait - to produce a genetically modified organism, one has to identify the trait which one wants the plant to have, and find out what other organisms already have it. This involves luck as much as careful searching. It also involves testing the plants themselves to find the most worthy subjects.

Step two: Grabbing genes - in the past, studying the genetic code of individual seeds required planting the seed, growing the plants to a certain size, and then clipping a paper-hole-puncher through a leaf to gather a sample. But that is a time-consuming and resource-heavy process, so it is easier to study the seeds themselves. This requires grinding them up, which is also inconvenient, because a ground-up seed cannot be planted.

[Picture Credit: Seed Chipper]



[Picture Credit: Close-up View of Seed Chipper]



To get around this, engineers invented a special chipping device that shaves off just a tiny piece of the seed and grinds it into a powder that can be analysed with genome-mapping technology.

Meanwhile, the viable remainder of the seed is preserved for planting and cultivation. The scientist now knows what genes are in the seed before it is in the ground. The chipper, which was patented last year, is a tool that provides a blast of air which separates the shavings from the rest of the seed; a bar code system ensures the two can be reconciled later. The device, about the size of a home air conditioner, can chip a seed every second. The chip is ground to a fine powder and analysed with an automated high-throughput genotyping system.

Step three: "Trait insertion" - now that one has the genes, the next step is inserting them into the plants. There are a couple ways to do this, including using "gene guns" that literally shoot pieces of DNA. A .22-caliber charge fires a metal particle coated with DNA into plant tissue. It is still widely used among some biotech companies.

[Picture Credit: Gene Gun 2]

For omega-3 soybeans, a slightly more delicate process is used - heating soybean seedlings to place them under stress and make them susceptible to a bug called *Agrobacterium tumefaciens*. The organism specialises in invading plant DNA and tricking it into producing sugars and amino acids that feed the bacteria. Scientists can exploit this 'Trojan horse' ability and insert new proteins into the plant's chromosomes. The plant recognises this foreign encoded protein as one of its own.



The pollen of the plant will now have that DNA in its genome, so when one has a pollination event and create new seed, that trait is advanced into the next generation - a first-generation genetically modified plant.

Step four: The growth chamber - after about two years of testing, the seedlings are weeded to a handful of potential winners in a growth chamber - then further weeded out to result in one special GM seed.



[Picture Credit: Growth Chamber]

The seedlings are then tested for drought tolerance, salt tolerance, pest and disease resistance, and more. Currently, plant biologists have to study their charges by hand, taking pictures of their roots and testing their viability.

Step five: Planting – a planter has been devised to plant the seeds according to specifications – the seeds are sown under cover of night if necessary. The planter has five separate seed boxes and can distinguish among different hybrid varieties, and it will remember exactly what plant was sown where, ensuring accurate data for use by the agronomic experts. The planter can sow seeds at variable speeds and spacing, providing a well-rounded picture of how plants grow in certain conditions.

Step six: The genes express themselves – new genes have been isolated, thousands of seeds were chipped to find strong candidate plants, candidate plants were grown in special chambers, under the ideal method in the ground. Now weeds must be prevented from stealing their nutrients, and keep pests from harvesting the crops. That is where genetically modified crops, that can resist herbicides and pests, come in.

Farmers who buy transgenic seeds are free to spray herbicide containing glyphosate on their fields throughout the growing season. This reduces the need for tilling and thereby prevents soil erosion. Glyphosate, the active ingredient, kills growing plants by preventing them from forming three particular aromatic amino acids, tryptophan, phenylalanine, and tyrosine.

To create 'glyphosate resistant' plants, a gene was cloned from a form of agrobacterium found growing at a Monsanto factory. Researchers found that this particular bug's amino production was not affected by glyphosate, and they used *E. coli* to clone the gene responsible for this trait. Then they

used a different agrobacterium - the familiar *A. tumefaciens* - to stick the gene into the chromosomes of plants. The plants that have the bacteria's gene are still able to produce the three amino acids, and they survive just fine. Weeds are not so lucky.

Agrobacterium is not the only bacteria used to make genetic modifications. "Bt" varieties of cotton and corn have been modified to produce a chemical that is toxic to insect larvae, and the gene that expresses that trait comes from a bug called *Bacillus thuringiensis*. (The gene is also inserted using the *A. tumefaciens* process.) Farmers need to plant "refuges," areas without their engineered insect-tolerant seeds, so that pests still have a place to feast and will be less likely to evolve resistance.

Studies have shown that Bt plant roots can leach Bt toxins into ground soil, however, and while Bt is a native bacteria, the plants' effects on the other soil flora is still relatively unknown. Bt cotton is widespread in China and India, the world's two largest cotton producers.

Glyphosate Tolerant Maize: An Example of Genetic Engineering

Glyphosate tolerant maize is genetically modified maize that has had its DNA modified to withstand the herbicide glyphosate. It is also sometimes referred to as 'Roundup Ready' maize (RR). RR maize was first deregulated in the United States in 1997 and first commercialised in the United States in 1998.

Glyphosate



Glyphosate (*N*-(phosphonomethyl) glycine) is a broad-spectrum systemic herbicide used to kill weeds, especially annual broadleaf weeds and grasses known to compete with commercial crops grown around the globe. It was discovered to be a herbicide by Monsanto chemist John E Franz in 1970. Monsanto brought it to market in the 1970s under the trade name *Roundup* and Monsanto's last commercially relevant United States patent expired in 2000. (Wikipedia).

[Picture Credit: John E Franz]

Glyphosate currently has the highest global production volume of all herbicides. The largest use worldwide is in agriculture. The agricultural use of glyphosate has increased sharply since the development of crops that have been genetically modified to make them resistant to glyphosate. Glyphosate is also used in forestry, urban, and home applications. Glyphosate has been detected in the air during spraying, in water, and in food. The general population is exposed primarily through residence near sprayed areas, home use, and diet, and the level that has been observed is generally low. There is limited evidence of carcinogenicity in humans for non-Hodgkin lymphoma following exposure to Glyphosate. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals.

Genetically Modified Maize

A major class of Genetically Modified Organisms (GMO), maize, in this instance, was engineered to be tolerant of the herbicide glyphosate. Glyphosate is a small molecule that inhibits an enzyme, 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which catalyses an essential step in the biosynthesis of the amino acids phenylalanine, tyrosine and tryptophan. EPSPS is, therefore, an enzyme that catalyses a reaction in plant and bacterial cells that is necessary for the synthesis of some amino acids.

By denying rapidly growing plants these amino acids, it is able to rapidly inhibit growth of plants onto which it has been sprayed. Glyphosate is generally considered to be inert in humans, who get these amino acids from their food, and do not have an EPSPS.

The obvious problem with using glyphosate to control weeds is that it will, under normal circumstances, also kill crop plants. However, plants that have been engineered to express an alternative form of EPSPS functions normally even in the presence of glyphosate. These plants are thus "Roundup Ready", and will survive doses of glyphosate used to kill weeds in the field (Michael Eisen).

5-enolpyruvylshikimate-3-phosphate (EPSP) synthase is an enzyme which catalyses the chemical reactions:

phosphoenolpyruvate + 3-phosphoshikimate \rightleftharpoons phosphate + 5-enolpyruvylshikimate-3-phosphate (EPSP)

Thus, the two substrates of this enzyme are phosphoenolpyruvate and 3-phosphoshikimate, whereas its two products are phosphate and 5-enolpyruvylshikimate-3-phosphate.

It is the biological target of the herbicide, glyphosate, and a glyphosate-resistant version of this gene has been used in genetically modified crops.

The enzyme belongs to the family of transferases, to be specific those transferring aryl or alkyl groups other than methyl groups. The systematic name of this enzyme class is phosphoenolpyruvate:3-phosphoshikimate 5-O-(1-carboxyvinyl)-transferase. Other names in common use include:

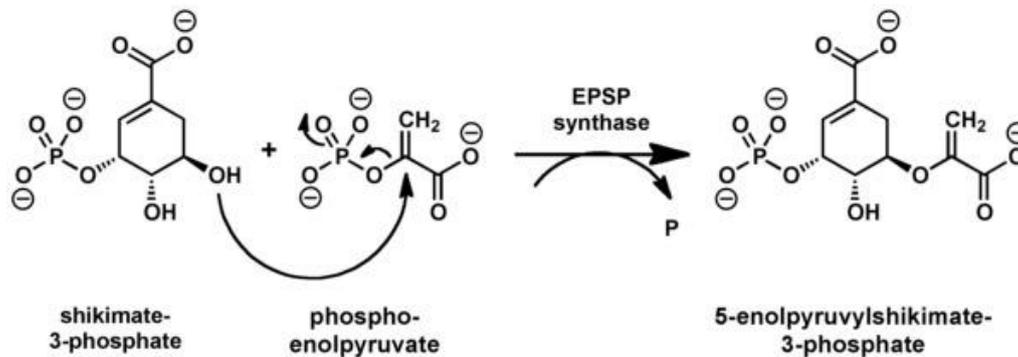
- 5-enolpyruvylshikimate-3-phosphate synthase
- 3-enolpyruvylshikimate 5-phosphate synthase
- 3-enolpyruvylshikimate acid-5-phosphate synthetase
- 5'-enolpyruvylshikimate-3-phosphate synthase
- 5-enolpyruvyl-3-phosphoshikimate synthase
- 5-enolpyruvylshikimate-3-phosphate synthetase
- 5-enolpyruvylshikimate-3-phosphoric acid synthase
- enolpyruvylshikimate phosphate synthase
- 3-phosphoshikimate 1-carboxyvinyl transferase

EPSP synthase is a monomeric enzyme. The molecular mass has been estimated from about 46 000 to 51 000. It is composed of two domains, which are joined by protein strands. This strand acts as a hinge, and can bring the two protein domains closer together. When a substrate binds to the enzyme, ligand bonding causes the two parts of the enzyme to clamp down around the substrate in the active site.

EPSP synthase has been divided into two groups according to glyphosate sensitivity. Class I enzyme, contained in plants and in some bacteria, is inhibited at low micromolar glyphosate concentrations, whereas class II enzyme, found in other bacteria, is resistant to inhibition by glyphosate.

EPSP synthase participates in the biosynthesis of the aromatic amino acids phenylalanine, tyrosine and tryptophan via the shikimate pathway in bacteria, fungi, and plants. EPSP synthase is produced only by plants and micro-organisms; the gene coding for it is not in the mammalian genome.

EPSP synthase catalyses the reaction which converts shikimate-3-phosphate plus phosphoenolpyruvate to 5-enolpyruvylshikimate-3-phosphate (EPSP).



EPSP synthase is the biological target for the herbicide, glyphosate. Glyphosate is a competitive inhibitor of the enzyme, acting as a transition state analogue that binds more tightly to EPSP synthase than its natural substrate and thereby prevents binding of substrate to the enzyme. This binding leads to inhibition of the enzyme and shuts down the entire pathway. Eventually this results in organism death from lack of aromatic amino acids the organism requires to survive.

A version of the enzyme that both was resistant to glyphosate and that was still efficient enough to drive adequate plant growth was identified by Monsanto scientists after much trial and error in an *Agrobacterium* strain called CP4, which was found surviving in a waste-fed column at a glyphosate production facility; this version of enzyme, CP4 EPSPS, is the one that has been engineered into several genetically modified crops.

Most glyphosate applications in Roundup Ready corn occur before the corn kernels start to develop; therefore, very little glyphosate is present in the kernels, so residues in the kernels are low. Typical Roundup Ready corn grain residues are well below one part per million (ppm). Levels this low do not pose any health concerns. Studies of Roundup Ready corn have shown that the amount of glyphosate in the corn plant following a foliar application drops fairly quickly, due to wash-off of surface residues, dilution as the plant grows and distribution throughout the plant and roots.

Regulation of Genetically Engineered Organisms in South Africa

The primary legislation in South Africa dealing with genetically modified organisms (GMOs), including their contained use, trial release, commercial release, and import and export is the Genetically Modified Organisms Act, 1997 (Act No 15 of 1997) (GMO Act) and its subsidiary legislation. This Act established three regulatory authorities—an Executive Council, Registrar, and an Advisory Committee—for effective implementation of its objectives.

The GMO Act places various restrictions on the research, production, and marketing of GMOs. For instance, it requires a permit for conducting most GMO-related activities, and conducting such activities entails putting in place scientifically-based risk assessment measures and notifying the public before the release of GMOs into the environment. If the EC deems it fit to do so, an applicant for a permit for a GMO-related activity may also be required to conduct an environmental risk assessment. The Act also requires the registration of all facilities where GMO-related activities take place. It further requires that safety to the environment be demonstrated before GMOs can be approved for release.

The GMO Act imposes civil liability on people who conduct GMO-related activities for damage they cause and criminalizes various acts, including violations of its provisions or refusing to cooperate with the regulatory bodies.

In addition to the primary legislation and regulatory institutions, South Africa also has in place other laws and institutions regulating specific issues relating to GMOs. The Department of Health, specifically the Food Control Section, tasked with the responsibility to ensure food safety in the country, has issued regulations requiring that foodstuffs obtained through certain genetic modification techniques be labelled as such before being offered for sale in the marketplace. Further labelling requirements are imposed by the Consumer Protection Act and its subsidiary legislation.

[Picture Credit: GMO Regulation]

Relative to other African countries, South Africa embraced biotechnology early on. The first field trials of genetically modified crops in the country were conducted in 1989. South Africa first approved the commercial release of genetically modified, insect-resistant cotton and maize in 1997.

Today, South Africa is the world's eighth largest producer of GMO crops. The statistics for the 2011–12 maize production season illustrate the scale of GMO penetration in the country.

[Picture Credit: Producers of GMO Crops]

During the period (2011-2012), genetically modified maize accounted for 79% (2.1 million hectares) of the commercial land planted with maize, with white maize accounting for 78% (1.3 million hectares) and yellow maize accounting for 81% (863 277 hectares) of the total maize planted in their respective classes.



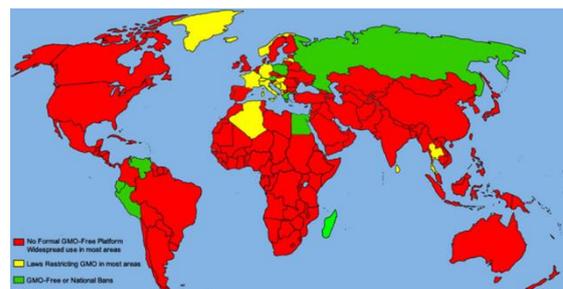
South Africa has a fairly vigorous regulatory regime governing various aspects of GMO use, including contained use, trial release, commercial release, and transboundary movement. The primary legislation governing the issue is the Genetically Modified Organisms Act, 1997 (Act No 15 of 1997) as amended (GMO Act) and its subsidiary legislation.

The GMO Act was amended in 2006 (although the amendment did not take effect until 2010) in part to give effect to the Cartagena Protocol on Biosafety, which South Africa ratified in 2003.

There are also a number of other laws imposing additional rules on GMO-related activities, including the National Environmental Management: Biodiversity Act (NEMBA), the Consumer Protection Act, and the Foodstuffs, Cosmetics and Disinfectants Act.

The Threat of Human Genetic Engineering

There is a real threat of human genetic engineering. The main debate around human genetics currently centres on the ethics of genetic testing, and possibilities for genetic discrimination and selective



eugenics. But while ethicists and the media constantly re-hash these issues, a small group of scientists and publicists are working towards an even more frightening prospect: the intentional genetic engineering of human beings.

Just as Ian Wilmut presented the world with the first clone of an adult mammal, Dolly, as a *fait accompli*, so these scientists aim to set in place the tools of a new techno-eugenics, before the public has ever had a chance to decide whether this is the direction we want to go in. The publicists, meanwhile are trying to convince the world that these developments are inevitable. The Campaign Against Human Genetic Engineering, has been set up in response to this threat.

Currently, genetic engineering is only applied to non-reproductive cells (this is known as 'gene therapy') in order to treat diseases in a single patient, rather than in all their descendants. Gene therapy is still very unsuccessful, and we are often told that the prospect of reproductive genetic engineering is remote. In fact, the basic technologies for human genetic engineering (HGE) have been available for some time and at present are being refined and improved in a number of ways. We should not make the same mistake that was made with cloning, and assume that the issue is one for the far future.

Medical Disclaimer

This Fact Sheet and Position Statement is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet and Position Statement. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet and Position Statement.

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