



Scientific background report AMFLORA potato



The Amflora potato in short

Amflora is a genetically modified potato variety of chemical company BASF. The potato has a modified starch composition. This potato produces only amylopectin, although potatoes by their nature produce a mixture of amylose and amylopectin. The Amflora potato is not fit for human consumption, but is solely grown for industrial applications. It is a so-called 'starch potato'. Amylopectin is used in the paper industry, the textile industry, in adhesives and in construction materials, among others.

Market approval of Amflora did not come easy. On March 2, 2010 the European Commission gave the final go-ahead for market introduction of the potato after a 13 year long procedure. Sore subject was the presence of the antibiotic resistance gene *nptII*. This gene protects the potatoes against the effects of antibiotics kanamycin and neomycin. The gene is used as a selection marker for creating the potato. In a first step, several genetically modified potato lines have been created. However, the modification is not taken up in all plants and the *nptII* gene allows for selecting plants that have taken up the modification in a simple way, which is to grow the potatoes during the modification process on a culture medium in which kanamycin is present. There was great concern about the possibility that the presence of the *nptII* gene could contribute to accelerated manifestation of antibiotic resistance in pathogenic bacteria. This concern turns out to be unfounded.

About this report

In this report the VIB ('Vlaams Instituut voor Biotechnologie' (Flemish Institute for Biotechnology)) provides an overview of the scientific knowledge of the Amflora potato. VIB is a scientific institution with 1200 employees, with research groups at UGent, K.U. Leuven, Universiteit Antwerpen and Vrije Universiteit Brussel. The Flemish government entrusted VIB with disseminating evidence-based information on biotechnology.

About the references

Added to every paragraph you can find the references to the publications from which information was used. Sometimes you can fully download these publications; sometimes they are not freely available. In the latter case you can ask the author or look up the publication in the nearest university library.

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Potatoes are cultivated worldwide

Potato cultivation is important. Potatoes are cultivated in more than 100 countries. In 2006 a worldwide total of 315 million tons of potatoes were produced, with an international market value of about 6 billion dollars. China and India together produce more than 30% of all potatoes.

Originally, potatoes come from the South American Andes. Explorers brought them to Europe. The Europeans failed to make use of the potato for many years, but at a given point they spread from Europe all over the world. Potatoes grow best in temperate climate zones. At temperatures under 10 °C and over 30 °C growth of the tuber is restrained.

Three types of growing potatoes can be distinguished: seed potatoes, consumption potatoes and starch potatoes. Growing seed potatoes is used for multiplying planting material. The Netherlands specializes in this field and exports planting material all over the world. Growing potatoes for human consumption is most important. It provides the potatoes we all eat, from potatoes for cooking to deep-frozen French fries, and of course snacks like chips. Starch potatoes produce starch for industrial applications: for adhesives, textile, paper, construction materials, etc. Starch potato varieties are specially selected for their suitability for producing starch for industrial applications. It is possible to eat starch potatoes, but they are not very tasty. Amflora is a starch potato.

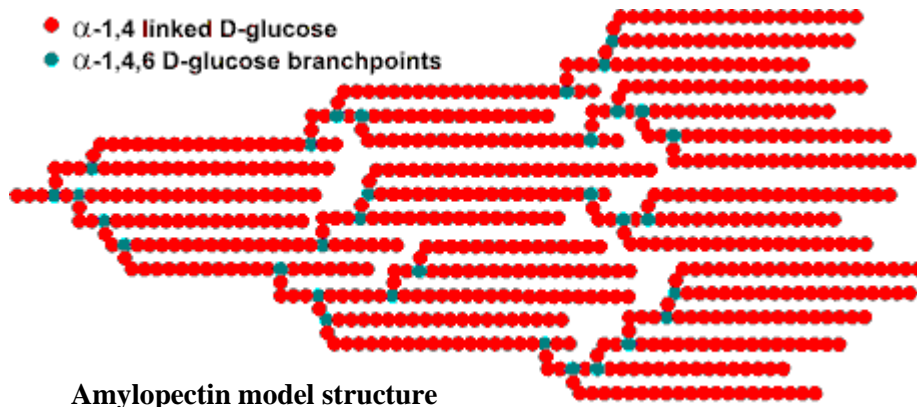
Starch potato production comprises only part of total potato production. In Europe this is about 220,000 ha of starch potatoes on a total of 1,250,000 ha, so 18%. The harvest of European starch potatoes represents a value of about 350 million euros. In Belgium no starch potatoes are grown. Cultivation of potatoes in Europe is concentrated in The Netherlands, Germany, France, Denmark and Sweden, but in the Czech Republic and Poland production takes place as well. Usually the starch potato fields are close to the factories that process them.

www.potato2008.org

The presence of amylose requires processing to make the starch suited for industrial applications and these processes are not environmentally friendly

Two forms of starch are present in potatoes: amylose and amylopectin. Usually about 20% is amylose and 80% is amylopectin. Both are glucose chains, but they differ in the way in which the glucose molecules are connected. This leads to different chemical properties. Amylose is an unbranched form. Amylopectin is a branched form, in which the branches result from so-called 'alfa 1-6' joints. As a result of this, amylopectin is characterized by a tree structure. Amylopectin

jellifies, amylose has a thickening effect. Due to the difference in properties, their application differs. For industrial applications only amylopectin is useful, and one would be happy to get rid of all the amylose from the starch fraction.



However, separation of amylose and amylopectin is labor intensive, energy consuming and therefore economically unfavorable. So in practice, for industrial purposes this is not done. Instead, the starch is chemically treated to modify the properties of the amylose present. This requires the use of energy and represents an ecological burden. Therefore, it would be useful for both environmental and economic reasons to have starch potatoes that only produce starch in the form of amylopectin.

The Amflora potato is genetically modified to stop amylose production

The Amflora potato is a genetically modified potato in which only starch of the amylopectin form is produced. To achieve this, scientists intervened in the biosynthesis of the starch. Various enzymes are involved in the biosynthesis of starch in a potato. The GBSS (granule bound starch synthase) enzyme is necessary for amylose production. When this enzyme is missing, only amylopectin is created.

BASF has created the Amflora potato by inserting an extra piece of genetic material that serves to shut down production of the GBSS enzyme. Strangely enough they have introduced a genetic construct that expresses GBSS for this purpose. In other words: they have introduced an extra *gbss* gene, of which one would logically assume that it would rather lead to enhanced production of amylose than of reduced production. However, the additional copy suppresses the expression of the natural *gbss* genes via a mechanism called 'co-suppression'. This is a mechanism that is naturally employed by the plant against invaders like viruses. This works in the following way:

In the natural situation

The cultivated potato is 'tetraploid' (every chromosome occurs 4 times) and therefore naturally contains 4 *gbss* genes. When *gbss* genes are expressed, first an RNA copy is made from these genes (an RNA copy is made from DNA). Then, the copy is transported to another place in the cell, where the various amino acids are put together based on the building block order of the RNA copy, to form the GBSS enzyme. The synthesized enzyme can then start its work and produce amylose.

In the Amflora potato

This process is interrupted in the Amflora potato. The additional copy of the *gbss* gene initiates a pathway that breaks up the RNA copies that have been made. And without RNA copies, no GBSS enzyme can be formed. As a result, no more amylose is synthesized.

It turned out that in the Amflora potato the additional *gbss* gene was present in the form of a head-tail double copy. Which looks like this:

→ ←
gbss - *ssbg*

In the genetic construct that was used for the modification, the gene had only a single presence, but in the transfer of the gene to the plant DNA it has been transferred twice and is built in as mirror image copy. That is why the Amflora potato now contains two additional *gbss* genes. That is, besides the 4 naturally occurring ones.

A second genetically modified starch potato is expected

AVEBE in The Netherlands also created a genetically modified potato variety in which only amylopectin is produced. This variety is called 'Modena' and the market application to allow cultivation in Europe has started its long march through the European regulatory world.

www.avebe.com

http://www.gentech.nl/alle_berichten/landbouw/avebe_vraagt_toelating_voor_teelt_modena

The Amflora potato contains the *nptII* antibiotic resistance gene

The Amflora potato not only contains the *gbss* gene, but the antibiotic resistance gene *nptII* as well. This gene causes resistance of the plant against the effects of antibiotics kanamycin and neomycin. The resistance gene has no function whatsoever in the resulting crop, contrary to the *gbss* gene. It is only present in the plant as a tool for the original modification. The gene serves as a selection marker that allows selecting only those plants that have incorporated the modification. Some explanation:

In order to create the Amflora potato, a genetically modified bacterium (*Agrobacterium tumefaciens*) is brought onto small pieces of potato tissue in a Petri dish. This genetically modified bacterium carries the *gbss* and *nptII* genes which are coupled in the same piece of DNA. This piece of DNA is transferred by the bacterium to the plant DNA after infection of plant cells. However, the piece of DNA is only incorporated by a few cells. By subsequently stimulating the potato tissue to grow on a culture medium in which the antibiotic kanamycin is present, only those plants carrying the *nptII* gene and demonstrating kanamycin resistance will develop. Plants that carry the *nptII* gene will carry the *gbss* gene as well, since the two are coupled in one and the same piece of DNA. So this is a very simple way to select only the genetically modified plants.

http://www.bioplek.org/animaties/moleculaire_genetica/transgeneplanten.html

Antibiotic resistance genes may cause risk

The use of antibiotic resistance genes may contain a risk for human health and the environment. Quite some diseases in man and animals are caused by bacteria. Take for example bacterial angina, pneumonia, or skin infections with *Staphylococcus aureus*, also

known as the bacterium that causes boils. These bacterial diseases are treated with antibiotics. But the use of antibiotics entails a risk. When bacteria are overused, bacteria can quickly become resistant. And the more bacteria become resistant, the more difficult it gets to fight them. Up to the point when we run out of means to take them on. In Flanders we still exert a strong selection pressure on bacteria to become resistant, even though the use of antibiotics has declined somewhat in recent years. Resistance can emerge in two different ways: by mutations in the bacteria (spontaneous changes in the genetic material) or as a result of bacteria adopting an existing resistance gene from their natural environment.

<http://www.microbiologie.info/resistentie.htm>

Resistant bacteria are a problem

Today, resistant bacteria are a big problem. Certain bacteria are resistant to such an extent that we hardly have any tools to fight them. Recent reports about the so-called 'bacteria with ESBLs' speak volumes. ESBL stands for extended spectrum beta-lactamase, in other words: resistant against all kinds of beta-lactamase antibiotics. It turns out that bacteria with ESBLs are often found in poultry subject to factory farming. Large amounts of antibiotics are preventively fed to the animals as growth promoter in this system. Another bacterium, the MRSA (methicilin resistant *Staphylococcus aureus*) has already gained notoriety many years ago. This bacterium is also very difficult to fight.

European antimicrobial resistance surveillance system <http://www.rivm.nl/earss/>

Does the Amflora-potato contribute to the emergence of resistant bacteria?

From a public health perspective we should ask the question whether, and if yes to what extent, the presence of the *nptII* antibiotic resistance gene in the Amflora potato contributes to the emergence of resistant bacteria. Three questions need to be answered in order to determine this:

- 1) Are the antibiotics against which the *nptII* gene provides resistance relevant for current human and veterinarian medicine?

The answer to this is YES. Kanamycin and neomycin are both characterized as "highly important antimicrobials for human use". Kanamycin is used as second-line antibiotic for treatment of multiple drug resistant tuberculosis. So caution is needed. The WHO is concerned about the growing resistance of tuberculosis against second-line antibiotics

like kanamycin. However, the *nptII* gene is not involved in this developing resistance. Apparently other genes that also provide resistance against kanamycin are responsible for this.

- 2) How big is the chance that a (medically relevant) bacterium incorporates an *nptII* gene from the potato and as a result of that becomes resistant against kanamycin and neomycin?

This chance is immensely small. Transfer of antibiotic resistant genes from transgenic plants to bacteria has neither been demonstrated in nature, nor in the laboratory. Only in the case that the bacterium already contains a part of the *nptII* gene, transfer could be perceived (as a result of so-called 'homologous recombination'). If DNA transfer of transgenic plants to bacteria would occur at all, than this would take place with an extremely low frequency in comparison with DNA transfer among bacteria.

Also, the *nptII* gene that is used as selection marker for creating transgenic plants is different than the *nptII* gene in bacteria. The gene has other regulatory signals ('ON/OFF switches'): regulatory signals that only work in plants. This means that if the *nptII* gene would be completely (regulatory signals included) transferred from a transgenic plant to a bacterium, it would still not work in that bacterium.

- 3) To what extent kanamycin and neomycin resistance has already spread in nature?

Recent scientific studies have shown that kanamycin and neomycin resistance is widely spread in bacteria and in the environment. The resistance turns out to be present in all environments that have been tested so far.

Consolidated presentation of the joint Scientific Opinion of the GMO and BIOHAZ Panels on the "Use of Antibiotic Resistance Genes as Marker Genes in Genetically Modified Plants" and the Scientific Opinion of the GMO Panel on "Consequences of the Opinion on the Use of Antibiotic Resistance Genes as Marker Genes in Genetically Modified Plants on Previous EFSA Assessments of Individual GM Plants", EFSA-Q-2009-00589 and EFSA-Q-2009-00593, EFSA, 2009
<http://www.efsa.europa.eu/en/scdocs/scdoc/1108.htm>

***NptII* in transgenic plants does not lead to development of resistance in bacteria**

Based on the above data, scientists conclude that – although kanamycin and neomycin are important antibiotics – the presence of the *nptII* gene in transgenic plants still does not lead to a higher chance of (medically relevant) bacteria developing resistance against these antibiotics. The chance that bacteria pick up resistance against kanamycin or neomycin from transgenic

plants is negligible compared with the chance that they pick up resistance from other bacteria. In other words: the use of *nptII* in transgenic plants has no significant effect on development of resistance in bacteria.

The Amflora potato is safe for cultivation

The Amflora potato is, besides its starch composition, agronomically similar to the variety from which it is derived. The potato is similar in disease susceptibility, similar in mode of reproduction, etc. One of the questions that have been raised concerning potatoes with a modified starch composition is whether such potatoes are better able to cope with night frost. In normal circumstances, night frost will kill off quite some of the potatoes unintentionally left behind on the field (by falling off the wagon, for example). Potatoes cannot withstand temperatures below -3°C . Only a limited fraction of the potatoes left behind emerge in the next crop as volunteer plants. Volunteer potato plants can pose a problem, as they can be a source for the spread of the potato disease late blight (*Phytophthora infestans*). An increased sensitivity for frost could imply increased survival and thus a bigger risk of the late blight of the potato. However, experiments have demonstrated that potatoes with a decreased level of amylose are not better suited to withstand night frost.

Opinion of the Scientific Panel on genetically modified organisms [GMO] on an application (Reference C/SE/96/3501) for the placing on the market of genetically modified potato EH92-527-1 with altered starch composition, for production of starch and food/feed uses, under Part C of Directive (EC) No 2001/18 from BASF plant science
<http://www.efsa.europa.eu/en/scdocs/scdoc/323.htm>

Various COGEM recommendations on genetically modified potatoes on: www.cogem.net

OECD Consensus document on the biology of potato

The Amflora potato cannot colonize the environment

Genetically modified plants should not have negative effects on the environment, such as pushing out existing species in nature or disturbing delicate natural balances. The Amflora potato does not have such properties. In Europe, the potato is absent as a wild plant. Besides that, the potato has no relatives in Europe with which it could outcross. This means that the genetically modified property cannot end up in the environment. The only possibility is that some Amflora potatoes occur as volunteer plants on a plot on which Amflora potatoes were planted or as volunteer plants in ground that came from a plot on which Amflora was planted.

Such volunteer plants are controlled in order to fight the late blight (*Phytophthora infestans*). Furthermore, cultivated potatoes have very poor competitive ability compared with other (wild) plants, preventing them from permanently colonizing our environment.

Traditional amylose-free starch potatoes are available on the market as well

In The Netherlands AVEBE put a traditional amylose-free potato on the market. This potato was made using 'mutagenesis' and is not covered by GMO legislation. The potatoes were created in the 1980s at the University of Groningen in The Netherlands by treating starch potatoes with X-rays. The radiation causes mutations (mistakes) in the genetic material of the plant, tens of them at the same time. After some research a potato line was discovered with a relevant point mutation in the *gbss* gene. The result was that the potatoes were unable to produce amylose any longer, but only amylopectin. These starch potatoes have entered the market in 2005 under the name 'Eliane'.

You may wonder why AVEBE is taking the trouble of obtaining market permission for the genetically modified Modena potato, while they already have the traditional amylose-free starch potato Eliane on the market. The reason is most likely that they can introduce into a potato the desired property in one step and without losing variety characteristics, while they lack that focus with traditional methods and often need to conduct many crossovers before arriving at a suitable variety. What perhaps also plays a role is that the Modena potato has variety characteristics that make it worthwhile (yield potential, disease tolerance, etc.).

www.avebe.com

<http://www.allesoverdna.nl/plant/voedsel/hoe-een-aardappel-prijzen-won.html>

In Germany traditional amylose-free starch potatoes have been developed as well

In Germany the Fraunhofer Institute for Molecular Biology and Applied Ecology (Fraunhofer IME) created starch potatoes that only produce starch in the form of amylopectin. The potatoes were made using mutagenesis, just like the AVEBE potatoes. However, in this case no X-rays were applied, but a mutagenic chemical (ethyl methanesulphonate). Then, the DNA of the generated potatoes was genetically screened to see whether they showed a mutation in the genes that are associated with starch synthesis. In this way they quickly found potatoes that

only produce starch in the form of amylopectin. The combination of chemical mutagenesis with targeted genetic screening is called “TILLING”: Targeted Induced Local Lesions in Genomes. The technology has also been applied to other crops like tomato. The Fraunhofer IME tomatoes are currently in the test stages and are not available on the market.

Traditional mutants are not necessarily more safe than genetically modified variants are

The Amflora, the Modena, the Eliane, and the potatoes of the Fraunhofer IME are all amylose-free potatoes. The difference is in the technology that is applied to arrive at this property. The former two are subject to GMO legislation; the latter two are not and are so-called ‘traditional’ variants. But which one is safer? Or is there no difference from a safety point of view?

In the Amflora potato an extra piece of DNA is present that settled at a random location in the potato genome. This extra piece of DNA contains the *gbss* gene and the *nptII* gene. The same applies for the Modena potato, with the only difference that the *nptII* gene is not present. The extra piece of DNA may have caused a mutation by its insertion into the genome, for example when it happened to land in an active piece of DNA (a gene). For the traditional amylose-free AVEBE potatoes and Fraunhofer IME potatoes we know that a mutation is present in one of the genes that are involved in the synthesis of starch. But because mutagenesis is a non-targeted technology in which not one but several mutations are introduced into the DNA at the same time, these potatoes will have other mutations as well. However, we do not know where those other mutations are and we do not know whether they have any effect, and if yes, which. When you look at the possible properties of the potatoes from a purely scientific point of view, there is no reason to assume that the traditional variants are necessarily safer than the genetically modified variants. The traditional amylose-free AVEBE potatoes and Fraunhofer IME potatoes are not free from uncertainties.

<http://www.fraunhofer.de/en/press/research-news/2009/12/super-potato.jsp>

Legislation makes a big difference

In legislation a strong differentiation is made between genetically modified and ‘traditional’ mutated potato variants. The Amflora potato from BASF and the Modena potato of AVEBE should pass through a strict trajectory and can only be introduced on the market when their safety for man and environment is proven. A European acceptance procedure applies, following

EU guideline 2001/18/EC and EU regulation 1829/2003. The traditional mutated AVEBE and Fraunhofer IME potatoes do not have to follow this procedure. If the potatoes are proven useful in variety tests, they are allowed on the market. To be clear: the Amflora should also pass these variety trials.

Before market introduction, the level of toxic glycoalkaloids is checked for all potatoes

Starch potato or not, genetically modified or not: The glycoalkaloid level of all new potato varieties is checked before they are allowed on the market. Glycoalkaloids are toxins that naturally occur in potatoes. In The Netherlands and Sweden an upper safety limit of total glycoalkaloid level of 200 mg/kg applies. Other EU countries have not specified glycoalkaloid limits. The presence of these toxins obliges us to peel potatoes before we can safely eat them. Furthermore, raw potatoes are very hard to digest. This is because they contain many substances that block our digestion enzymes. Heating potatoes will neutralize these substances.

The Amflora potato is not for human consumption

The Amflora potato is only grown in order to use the produced amylopectin in non-foodstuffs. For this purpose the potato is monitored by BASF from planting through processing by means of an 'Identity Preservation System'. Potato pulp and juice can only be processed in animal feed. And an accidental presence of the Amflora potato under 0.9% (of the potato share) is allowed in foodstuffs and animal feed. So it is especially due to this use in animal feed and possible accidental human consumption that the glycoalkaloid level of the Amflora potato has been determined as well.

An accidental presence of Amflora potatoes in another batch of potatoes under 0.9% is not required to be reported on the product label.

Should you accidentally eat an Amflora potato, no harm will be caused. When assessing the market acceptance file, accidental consumption is taken into account. A full food safety assessment has been performed. The conclusion was that the Amflora potato is just as safe as any other regular potato.

A 13-year procedural trajectory full of obstacles

The European market application file for the Amflora potato was submitted in 1996. The acceptance procedure was started, but in 1998 the file was hit by a *de facto* European moratorium on market authorisation of genetically modified crops. A number of European member states blocked further approval of market authorisation files and only wanted to continue taking authorisation decisions once European GMO legislation would be amended on a number of points. These amendments followed a number of years later. In 2001 the new 2001/18/EC Directive concerning environmental risks of GMOs was published and in 2003 the new Regulations 1829/2003 and 1830/2003 concerning food and animal feed safety and labeling of GMOs, respectively. In 2003 and 2005 BASF resubmitted its Amflora files adapted to the new legislation. The *de facto* European moratorium ended in 2004.

In 2006 the European Food Safety Authority (EFSA) issued two reports in which they stated that the Amflora potato is safe, both from an environmental perspective and from a food safety perspective. Then, the environmental application file was voted on in the Standing Committee for the Food Chain and Animal Health according to legal procedures. Because this vote failed to achieve a 'qualified' majority in favor or against, the file was sent to the European Council of Ministers so they could decide on it. There as well, however, voting failed to reach a conclusion. As a result, the file returned to the desk of the European Commission. The EC was then to decide, as is prescribed by the 'Comitology procedure'. This procedure states that when the member states fail to reach a conclusion, the European Commission should decide. The same happened with the food safety file. This file also returned to the desk of the European Commission.

However, the European Commission failed to settle the matter. It first asked the European Medicines Agency (EMA) its opinion on the use of *nptII* as selection marker in plants. Their report was published in February of 2007. In it, the EMA provided an overview of the importance of the use of antibiotics kanamycin and neomycin. However, the EMA failed to make conclusive statements about the amount of risk of the *nptII* gene being incorporated into bacteria from plants. For that the agency referred to the EFSA recommendations.

Commissioner for the Environment Stavros Dimas kept hesitating and wanted more certainty. That is why in 2008 he asked the EFSA to provide an additional consolidated advice on the use of antibiotic resistance markers in plants. As previously stated, the Amflora potato contains an *nptII* antibiotic resistance gene that provides resistance against antibiotics kanamycin and neomycin.

On June 11, 2009 the EFSA published its final advice on the use of the *nptII* gene in plants. In it, the EFSA finally concluded that the presence of the *nptII* gene in plants is not problematic. This meant that three positive EFSA reports were on the desk of the European Commission at that moment. In the end it was not Stavros Dimas, but the new Euro commissioner John Dalli who gave the green light for cultivation and processing of the Amflora potato on March 2, 2010.

In 2010, the Amflora potato is grown on 250 ha of land: 20 ha in Germany (in the Land of Mecklenburg-Vorpommern), 80 ha in Sweden and 150 ha in the Czech Republic. The amylopectin of the 150 ha of Amflora in the Czech Republic will be processed in industrial products. The other potatoes are grown for multiplying planting material.

http://ec.europa.eu/food/dyna/gm_register/index_en.cfm

<http://www.basf.com/group/corporate/en/products-and-industries/biotechnology/plant-biotechnology/amflora>

Opinion of the Scientific Panel on genetically modified organisms [GMO] on an application (Reference EFSA-GMO-UK-2005-14) for the placing on the market of genetically modified potato EH92-527-1 with altered starch composition, for production of starch and food/feed uses, under Regulation (EC) No 1829/2003 from BASF plant science

<http://www.efsa.europa.eu/en/scdocs/scdoc/324.htm>

Opinion of the Scientific Panel on genetically modified organisms [GMO] on an application (Reference C/SE/96/3501) for the placing on the market of genetically modified potato EH92-527-1 with altered starch composition, for production of starch and food/feed uses, under Part C of Directive (EC) No 2001/18 from BASF plant science

<http://www.efsa.europa.eu/en/scdocs/scdoc/323.htm>

Presence of antibiotic resistance marker gene npt-II in GM plants for food and feed uses, EMEA, Committee for medicinal products for veterinary use and Committee for medicinal products for human use, 22 February 2007