The use of antibiotic resistance marker genes in GM plants

ACNFP

THE ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

The use of antibiotic resistance marker genes (ARMs) during the production of genetically modified (GM) crops for food purposes has continued to be an issue of debate. This fact sheet explains how and why these genes are used in GM crop production and what is being done to ensure that foods derived from them are as safe to eat as conventional foods.

What are antibiotics?

The majority of antibiotics are natural products found in the environment, and are obtained from bacteria or fungi. Some antibiotics can also be synthesised or chemically modified in the laboratory, to make production easier and to increase their effectiveness. Some of the antibiotics available today have long been in widespread medical use. For example, penicillin has been used since the Second World War.

How do antibiotics work?

Antibiotics act by attacking specific "target sites" in micro-organisms. Even at low concentrations they can inhibit the growth of, or kill target micro-organisms. Therefore, they are often used as drugs to treat infections caused by bacteria. The "target sites" for antibiotic action are absent from humans, which is why we can take antibiotics safely.

What is antibiotic resistance?

Antibiotic resistance results when a micro-organism becomes no longer sensitive to the effects of a particular antibiotic compound. This may reduce the effectiveness of antibiotics used to treat infections.

How does antibiotic resistance occur?

Antibiotic resistance arises naturally in the environment when genetic changes in a micro-organism alter the target for the antibiotic, or enable the micro-organism to inactivate the antibiotic. Genes that give resistance to antibiotics can spread very rapidly through populations of bacteria. Resistant organisms were present in the environment long before humans discovered and started to use antibiotics. However, the intensive use of antibiotics in human medicine, and the use of antibiotics in farm animal feed, has resulted in an increase in the numbers of resistant bacteria, including those which are resistant to more than one antibiotic.

What is genetic modification (GM)?

Genetic modification involves changing a gene or inserting a new gene for a particular characteristic (or trait). In the case of GM crops, the modified or inserted gene is selected to give a specific desirable trait to the plant, e.g. resistance to pests, tolerance to herbicides or delayed fruit softening. The new gene may or may not be from the same species.

How and why is antibiotic resistance used in the production of GM crops?

The antibiotic resistance genes that are used in the production of GM crops are usually derived from micro-organisms. Although these genes have evolved to function in micro-organisms, scientists have found that they are a useful tool during the production of GM plants. During the genetic modification process, a gene providing resistance to an antibiotic can be inserted into GM plants as a marker, which is linked to the new gene with a desirable trait. Scientists can then use this marker to select the insertion of the new gene. In some GM crop varieties, antibiotic resistance genes are used at an earlier stage in the process, when genes are being assembled for insertion into the plant. This is normally done using micro-organisms but the resistance gene may then be carried through the process so that it is present in the GM plants.

What ARMs are currently used?

ARMs are not always used in the production of GM crops but, where they are in use, certain well-established genes are involved. One ARM that has been widely used in the development of GM crops is the gene providing resistance to kanamycin. Bacterial resistance to this antibiotic is common and this antibiotic is no longer used to treat humans and has limited veterinary use. Therefore, even in the unlikely event that other micro-organisms acquired resistance to kanamycin from GM plants, this will have no impact on human health.

Another ARM gene that has been introduced into GM plants provides resistance to ampicillin. Due to the intensive use of ampicillin and similar drugs in human medicine, many micro-organisms are now resistant to this antibiotic. Also, a large number of people have gut bacteria that carry the ampicillin resistance gene. Therefore, even in the unlikely event that micro-organisms acquired resistance to ampicillin from GM plants, the effect on the overall frequency of ampicillin resistance would be insignificant.

Why has there been debate about the use of ARMs?

The use of ARMs has been a controversial issue because it has been suggested that there may be the potential, under certain conditions, for these genes to transfer from the GM plants to bacteria that cause infections in humans or animals, thus compromising the medical or veterinary effectiveness of the antibiotics.

What action has the ACNFP taken to address these concerns?

The ACNFP identified possible food safety issues that might arise from the use of ARMs in food and published a report of their considerations in 1994. The report concluded that the only significant concerns were the potential for ARM genes transferring to gut bacteria and the chance that the bacteria may then become resistant to the associated antibiotic. However, the possibility of such events occurring was considered to be unlikely and independent research has confirmed that this is the case. The 1994 report also set out a number of recommendations and concluded that the safety assessment of foods from GM plants and other GM organisms that contain ARM genes should be evaluated on a case-by-case basis.

Having gained further experience from evaluating a number of foods derived from GM organisms, the ACNFP produced a follow-up report in 1996. This defined in detail the principles on which the ACNFP bases its safety assessment of ARM genes in GM food organisms. The report also confirmed that the probability of the transfer of ARM genes and the medical use of the relevant antibiotics are key factors in the evaluation.

What else is being done to ensure that foods that are derived from GM crops are as safe as conventional foods?

On the ACNFP's advice, previous Government-funded research has investigated the extent and conditions under which such gene transfer could occur. A 2003 review by an expert panel considered all of the available science behind concerns relating to GM crops, including the issue of gene transfer to non-plant species. It was recognised that there is potential for transgenic (GM) DNA to be transferred to organisms other than those from which it originated, but also that non-GM DNA would also have a similar fate. The transfer of transgenic DNA from GM plant material to bacteria has been shown to be unlikely to occur. Animals fed on GM plants readily digest DNA, including that which makes up antibiotic resistance genes. Although this process may be incomplete it is unlikely that these antibiotic resistance genes would be able to "escape" into the environment through this route, due to a series of well-established barriers.

During the initial period of uncertainty over the safety of ARMs, target dates were set for the phasing out of ARMs which were thought to have the potential to have adverse effects on human health and the environment. These dates are December 2004 for GM crops placed on the market and December 2008 for GM organisms authorised for experimental release in field trials.

In April 2004 the European Food Safety Authority's (EFSA's) Scientific Panel on Genetically Modified Organisms issued a detailed opinion on the wide scale use of antibiotic resistance genes as marker genes in genetically modified plants, including consideration of environmental risks. EFSA concluded that ARMs should be assigned to 3 groups based on the prevalence of resistance to the antibiotic amongst bacteria, extent of use of the antibiotic and clinical importance.

- *Group 1*: safe for use in field experiments and placing on the market
- *Group 2*: use should be restricted to field trial purposes only
- *Group 3*: should not be present in any GM plants

What is the ACNFP view on the use of ARMs?

The Committee endorses EFSA's opinion on the wide scale use of ARMs. The ACNFP has also considered this issue from a food perspective and notes that particular antibiotics have been useful in their role as selective agents in the development of GM crops. The Committee is of the opinion that the classification of ARMs for use in GM plants used in food production should be based primarily on the current level of resistance in the environment as clinical use varies throughout the world and may change over time. The ACNFP considers that only 2 classifications are needed in terms of food use.

- *Group 1*: ARMs that might be tolerated in food, coding for resistance that is common in the environment, or for resistance to antibiotic compounds that are very unlikely to be used in clinical application e.g. kanamycin resistance.
- *Group 2*: ARMs that should not be present in food, coding for antibiotics that are in clinical use and/or where resistance is rare in the environment.

The risks from ARMs have been identified as unlikely. However the ACNFP strongly urges that the use of ARMs in the development of new GM crops is limited to existing, well-established markers that are known to be common in the environment and have limited clinical significance.

Further information on the work of the ACNFP can be obtained by contacting the ACNFP Secretariat at the address below.

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