# REPORT OF THE SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION ON THE SUPPLEMENTARY QUESTION 88 CONCERNING NEW DATA SUBMITTED BY AUSTRIAN AUTHORITIES ON THE SAFETY FOR ANIMALS OF CERTAIN GENETICALLY MODIFIED MAIZE LINES NOTIFIED BY CIBA-GEIGY IN ACCORDANCE WITH DIRECTIVE 90/220/EEC FOR FEEDINGSTUFF USE

**(Opinion expressed the 10 April 1997)**

## TERMS OF REFERENCE (6 March 1997)

The Scientific Committee for Animal Nutrition (SCAN) is requested to express its view on the following questions:

1. Does the information provided by Austria (See background and Annex I) constitute new relevant scientific evidence which was not taken into account by the Committee at the time that its opinion on Question 88 was delivered?

2. Would this information thus cause the Committee to consider that this product constitutes a risk to human health of the environment?

## BACKGROUND

1. Council Directive 90/220/EEC[1] of 23 April 1990 on the deliberate release into the environment of genetically modified organisms establishes provisions to protect human health and the environment when placing on the market products containing, or consisting of, genetically modified organisms intended for subsequent deliberate release into the environment.

2. On 15 March 1995 the Commission received a notification by the company Ciba-Geigy concerning the placing on the market of genetically modified maize, forwarded by the French competent authorities. The competent authorities of seven Member States raised objections on various grounds.

   In accordance with the procedure laid down in Article 21 of Directive 90/220/EEC the Commission submitted to the Regulatory Committee established by Directive 90/220/EEC a Proposal for a Commission Decision by written procedure on 8 March 1996. This proposal sought to grant consent for the placing on the market of the genetically modified lines and any other maize (progeny) derived from crosses of these lines with traditionally bred maize.

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1 (O.J. No. L117, 8/5/90 p. 15) As modified by Commission Directive 94/15/EC of 15 April 1994 adapting to technical progress for the first time Council Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms (O.J. No. L103, 22/4/94 p. 20)

3. On 11 April 1996 the Regulatory Committee foreseen by Article 21 failed to deliver an opinion on the measures proposed by the Commission. The objections of the Member States which relate to animal health concern the safety of the prokaryotic *bla* (beta-lactamase) gene introduced in the plant genome under the regulation of a prokaryotic promotor.

4. Following the failure of the Regulatory Committee to deliver an opinion, the Commission forwarded to the Council a Proposal (COM/96/206 final) concerning the measures to be taken. The measures included in the Proposal for a Council Decision were identical to the ones presented to the Committee.

5. At the Environment Council of 25 June 1996 the Presidency concluded that the Council had drawn no conclusions and that this would allow both the French Government and the Commission to reflect on the issue.

6. Since Austria had provided further information concerning the safety of this genetically modified maize, on 24 July 1996 the Commission decided to ask three existing Scientific Committees to confirm the scientific basis of its Proposal. These Committees are the Scientific Committee for Animal Nutrition, the Scientific Committee for Food and the Scientific Committee for Pesticides.

7. An opinion on Question 88 was delivered by the SCAN at its 105th Plenary meeting on 13 December 1996.

8. On 14 February 1997 the Austrian competent authorities (Ministry of Health and Consumers Protection), after reevaluation of all documents concerning the mentioned notification, and taking also into account the results of a very detailed scientific discussion, informed the Commission that the marketing of Ciba-Geigy Maize in Austria has been prohibited by an ordinance, which entered into force on 14th February 1997.

   This action has been taken in accordance with Article 16 of Council Directive 90/220/EEC[2] of 23 April 1990 on the deliberate release into the environment of genetically modified organisms (See Annex II).

9. Austria considers that this product which has been properly notified and has received written consent with Directive 90/220/EEC constitutes a risk to human health and the environment. In support of the above, a document entitled "Reasons for Austria's decision to prohibit the use and sale of modified maize lines notified by CIBA-GEIGY for which a consent was given by France" has been provided to the Commission (See Annex I).

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2 (O.J. No. L117, 8/5/90 p. 15) As modified by Commission Directive 94/15/EC of 15 April 1994 adapting to technical progress for the first time Council Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms (O.J. No. L103, 22/4/94 p. 20)

**REPORT OF THE COMMITTEE** (10 April 1997)

At the 107th plenary meeting of the SCAN (Brussels, 10-11 April 1997), the Committee examined the documents under "References". It was asserted that in order to introduce a monitoring programme for evolution of Beta-lactam resistances as a result of the feeding of the GM-maize to animals a suitable marker for the GM-maize-derived ampicillin resistance is necessary. Dr. Franklin put express that the occurrence of beta-lactam resistance is very low in Sweden. It was also pointed out that the effect of the Bt toxin was dealt by the SC for pesticides, and looked mostly to the agronomic aspects.

The SCAN agreed that the information provided in the new publications does not constitute sufficient grounds for the SCAN to change the opinion given at the 105th plenary meeting (13 december 1996).

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SCAN/97/39 (Confidential) Question 88: Comments on new data by Austria

SCAN/97/40 (Confidential) Question 88: Comments on new data by Austria

SCAN-info97-10 Report on the review of Directive 90/220/EEC in the context of the Commission's communication on biotechnology and the white paper by the Commission of the European Communities

SCAN-info97-12 Regulation of the European Parliament and the Council concerning novel foods and novel food ingredients.

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**Reasons for Austria's decision to prohibit the use and sale of modified maize lines notified by CIBA-GEIGY for which a consent was given by France**

## 1. Introduction

In the evaluation of the CIBA maize dossier for a notification according to directive 90/220/EEC the majority of European Competent Authorities have expressed serious concern mainly related to the problems of the presence of the ampicillin resistance gene, possible hazards induced by an uncontrolled induction of resistance against the BT- protein, the unclear possibilities of the use of the herbicide resistance as well as insufficient labelling requirements.

In particular scientists of the ACNFP (Advisory Committee on Novel Foods and Processes), an advisory body to the British Ministry of Agriculture, Fisheries and Food, suggested to remove the antibiotics resistant gene from the particular maize product before being planted out as forage crop.

The genetic product of the antibiotic resistance "*bla* gene" is an enzyme that inactivates important antibiotics used in clinical and veterinary medicine. Although the *bla* gene is not expressed in the maize itself, the bacterial regulatory sequences could make it functional if it was transferred to other bacteria, especially to bacteria of the intestinal tract of humans or animals. Even if the probability of such a genetic transfer is low, the risk of spreading the antibiotics resistance is unacceptable. This risk arises especially from the plans to use the maize as non-processed forage. The-application does not provide an analysis of the relevance of such events in the case of the particular product and under special consideration of the *bla* gene".

For an evaluation of the discussed risks the European Commission has asked the scientific committees for Food (SCF), for animal nutrition (SCAN) and for pesticides for scientific advice. These committees hate thoroughly discussed.the problems and additionally. invited external experts for contribution. Recently opinions of the committees have been finalised. Generally there have been "no statements in respect of the safety of this product", by this indicating no foreseeable risks. Briefly, the committees have found that

- the probability of a gene transfer of a functional bla- construct into bacteria is zero and would have no clinical significance because of the narrow spectrum of resistance and the.existing distribution in natural bacterial strains (SCAN).

  The SCF considers a risk of bacterial transformation as extremely low and the risks that the product would add significantly to the already widespread occurrence of ampicillin resistant bacteria in animals and

man is remote but proposes to scrutinise the future needs arid application of marker genes.

- the transgenic maize is, except for the inserted traits, substantially equivalent to the parent plant and it is unlikely that the genetic changes introduce any new potential for allergenicity.

- a possible development of insect resistance to the BT- toxin would not have an adverse effect on the environment because it would not allow the BT resistant cornborer to cause any adverse effects that is not already associated with the nonresistant cornborer. Development of insect resistance to the BT toxin would be mainly an agricultural problem which can be dealt with existing pest control and agronomic methods

By this, the experts of the scientific committees have extensively reviewed the discussed problems. All the scientific comments and arguments are valid and well taken.

However from the Austrian point of view especially new scientific results have questioned the present scientific possibility of a conclusive evaluation of the mechanism of gene transfer as well as the development of resistance to the B.t. toxin.

Accordingly possible risks are very hard to assess and should be avoided at the present state of the scientific discussion.

**2. Assessment of the b-lactamase resistance:**

Clearly, degradation and digestion would have to be expected for DNA released from plant material. But recent results show unexpected long survival of DNA under specific conditions (Lorenz and Wackemagel, 1994, Webb and Davies, 1994). Mechanisms of adsorption and release of DNA from particles are not well understood. Specific results indicate that DNA can even pass the gastrointestinal tract without being completely degraded (Schubbert *et al*., 1994)

Proficient information is available about mechanisms and requirements for bacterial competence and transformation *in vitro* but only limited information is available for the evaluation of these mechanisms and their relevance in specific natural habitats (e.g. Bauer *et al.,* 1996; Ogunseitan, 1995) Also transfer of plasmids has been shown to mouse intestinal bacteria (Igimi *et al.,* 1996). Moreover, a potential role for a gene transfer among bacteria in the intestinal tract induced by transduction needs to be evaluated as very limited information is available about the factors which can be exchanged in physiological situations.

The host range of the relevant pUC plasmid is limited, but could include bacteria in the intestine of humans and animals. Very little information is as yet available for the spread of the plasmid (Sharma *et al.,* 1993). Also a

disadvantage of strains carrying high copy number plasmids has been seen under defined conditions but in a natural situations different selective pressures might be relevant for the establishment of the genetic information.

Because of the requirements of a homologous recombination a horizontal gene transfer seems highly unlikely and only limited to evolutionary processes (Heinemann, 1991). Surprisingly, recent investigations have shown increasing evidences for a horizontal gene transfer in model systems (e.g. Syvanen, 1994; Courvalin *et al.,* 1995) as well as a possible gene transfer from plants to micro-organisms (Hoffmann *et al*., 1994).

Phage DNA added to food supply of mice could even be traced in somatic cells (Doerfler and Schubbert *et al.,* 1997).

Given the current uncertainties about naturally occurring gene transfer mechanisms more information s are necessary for a conclusive evaluation of the significance and relevance of such events. Significance of a horizontal gene transfer in risk terms may be realised if the genes confer a selective advantage to the recipient organism (Harding, 1996) such as resistance to antibiotics.

Also the impact of a potential gene transfer of the bla-gene/b-lactamase and a potential induction of resistance in bacteria on the therapy of humans and animals with antibiotics remains rot fully conclusive. The degree of naturally occurring antibiotic resistance's as well as the mechanisms of maintenance and transfer of the natural resistance may not apply to the development of antibiotic resistance imposed by resistance genes artificially introduced in high amounts in natural habitats.

Normally ampicillin resistance is found on a wide variety of plasmid type of resistant isolates and recently. transferable ampicillin resistance associated with resistance to other antibiotics (Trimethoprim, Streptomycin, tetracyclin, spectinomycin, gentamycin and others) could be demonstrated raising the possibility that the use of any of these agents, not simply ampicillin, may contribute to the maintenance of resistance genes (Shanahan *et al.,* 1995). In case of a transfer of gene fragments of the modified maize containing tile bla gene ways of integration and stability are difficult to assess and effects of an selective pressure under therapy can not be easily compared with conventional situations. More information addressing the relevance of transposons in the spread of antibiotic resistance genes would also be necessary in this respect (Salyers *et al.,* 1995).

Furthermore, effects of ampicillin resistance on the activity of modern b-lactam antibiotics like cephalosporins arc well known (Georgopoulos, 1997) By this, also the impact of an transfer of the bla gene to bacteria of humans ore animals can not be fully evaluated especially in situations of an concomitant antibiotic treatment.

## 3. Assessment of the Bt Toxins and a resistance development.

Naturally found toxins from soil bacteria such as *Bacillus thuringiensis* count as environmentally friendly pesticides therefore "B t. substances' have been used in agriculture -including organic farming - for several decades. They are a mixture of *Bacillus thuringiensis* bacteria their spores and/or the toxin crystals themselves

So far no side-effects of "Bt. substances" have been registered, because the bacterium has a comparably long reproductive cycle in soil and can, for example, be inactivated by ultraviolet light. Besides, the substances are not used constantly but only when necessary. Commercially available substances do not contain active toxin but inactive protoxin that has. to be activated in a multistage process (solution by alkaline pH > 9-10, breakdown by digestive enzymes of insects).

The toxin's protein crystals are called "*Cry*" proteins, the corresponding genes "*Cry*" genes. Today about 50 "*Cry*" proteins are known with sequential and specific differences for certain insects (Höfte and Whitley, 1989).

The introduction of cry genes to crop plants (e.g. cry M b in the particular maize product) may cause the following situations that differ from the conventional use of "B.t. substances" (Hokkanen and Deacon. 1994; Milner, 1994): permanent production of toxins; expression of toxins in all parts of the plant; and development of a modified (shortened) variant compared with the protoxin.

If plant material gets into the soil, there may be higher concentrations of "B.t. toxin" compared with conventional use. These concentrations can exceed inactivation and breakdown. The resulting accumulation may influence non-target organisms negatively or speed up the selection of resistant target insects. New scientific findings prove that "B.t. toxin" combines with soil components and that it is able to survive in soil while maintaining and even Increasing its biological activity (Tapp and Stotzky, 1995). This makes the above scenarios even more probable.

The qualitative and quantitative differences of the use of genetically modified plants expressing "B.t. toxins" in comparison with the conventional use of microbial "B.t. substances" were not considered sufficiently in the application.

In the EU application there are no data concerning the toxicity of maize expressing *cry* IA (b) for a species of collembola (*Folsoma candida*) that were considered In the US procedure. The avoidable summary describes the toxic effect on the tested species but gives no comprehensible reason why this effect is negligible in Practice.

Possible Indirect Effects through Resistance Development:Possible Indirect Effects through Resistance Development:

So far "B.t. toxins" have been sprayed on plants where they were broken down under the influence-of light within a few days. By contrast, the toxins in transgenic p,ants are produced continuously and not according to necessity. Moreover, the concentration cannot be measured in exact doses and so far only one variant has been produced, but no mixture. Often there is no tissue specific expression in all parts of the plant. This not only increases the efficiency of the toxin but may also speed up the resistance development of pest insects (Roush 1994; Gould, 1994). Even the US, where there is often no strictly critical approach towards genetic engineering, has imposed certain conditions before authorising the introduction of "B.t. maize" products by companies like Giba-Geigy/Novartis and Northrup King/Sandoz/Novartis (EPA 1995a; EPA 1996).

Incomprehensibly, the proposal of the Commission decision does not provide for a resistance management programme to reduce resistance development in pest insects. This means a stop backwards compared to the US in terms of safety for the environment and human health.

In autumn 1995, the American EPA authorised the introduction of genetically modified insect resistant cotton by the company Monsanto over a limited period of 5 years (EPA 1995b). The cotton expresses the cry IA (c) gene of *Bacillus thuringiensis* that shall have a toxic effect on the cotton bollworm and two other cotton pasts (pink bollworm and tobacco budworm). In addition to the time limit a number of conditions were imposed for authorization to safeguard a state-of-the-art resistance management programme.

In the 1996 growth period the, product was planted out in the US for the first time. There are, however, reports about a bad infestation of cotton bollworm in the Texan cotton plantations of the new product (Macilwain 1996; Kaiser 1996). At the moment the company - together with the EPA and scientific advisers - tries to find out the reasons for this development. Scientific conclusions shall then bc put into practice. There are several possible reasons:

Extraordinary climatic conditions (temperature, etc.) led to an increased reproduction of the pest insects; an unstable expression led to an inactive "B.t. toxin"; resistance development In the pest insects within an extreme short period together with an Inefficient resistance management programme.

As long as there Is no light cast on the background and causes of the unexpected development In Monsanto's "B.t. cotton", it is incompatible with the precautionary principle to authorise an EU-wide introduction of Ciba-Geigy's "B.t. maize".

If a fast resistance development of pests is found as cause, the approach towards "B.t. plants" needs a fundamental rethinking (Whalon and Norris, 1996). A minimum requirement would be the development of an elaborate resistance management programme involving industry, scientists, farmers

and authorities, which in turn had to be laid down as precondition In the Commission decision.

## 4. Conclusions:.

On the basis of the present scientific knowledge the possibility of a transfer of the bla-ampicillin resistance gene to bacteria of the intestine of humans or animals under various conditions which then could cause a harmful clinical impact is very low. However, the scientific- evaluation of possible risks can not be conclusive, as many relevant mechanisms are not fully understood or investigated by now.

Furthermore, the highly unlikely risks have to be compared to the fact that high amounts of plant material containing the relevant gene will be given to humans and animals for a long time after an admission of the product to the market. One has also to realise that this product contains the discussed ampicillin resistance gene as well as one more herbicide resistance marker gene which is not any longer state of the art for the production of genetically modified plants. There are adequate maize products already available which do not comprise these restrictions and by this there is no reason to accept risks which are difficult to assess.

Even more questionable seems the possibility of a further scenario where the product, admitted to the market could be the basis for a further breeding which ten would lead to products which contain marker genes without any need for admission, control or labelling related to the genetic modification.

Addressing the problem of resistance development it seems questionable if resistance development is just only an agricultural problem which can be solved with other and additional pest controls. Good agricultural practice should pay attention to both, target agricultural areas and non-target eco-systems and try to avoid the need of necessary additional pest control measures. In any case, resistance management programmes have been specified in the admission documents of similar products, are common practice in the US-EPA admissions and have to be laid down as precondition in the Commission decision for the discussed product.

The Austrian Act on genetic engineering (Österreichisches Gentechnikgesetz) which entered-into force on 1st Jan., 1995 has established the principle of precaution (§ 3)

as a fundamental principle to be applied when implementing this act. This principle is also well established in the directive 90/220/EEC. In the case of modified maize lines notified by CIBA-GEIGY both the ampicillin resistance as well as the resistance against the B.t. toxin without any legally binding resistance management programme are in a conflict with this principle of precaution and the present state of the art for the development of genetically modified crops.

**Literature**

(See under references)

ANNEX II

ARTICLES 16 AND 21 OF COUNCIL DIRECTIVE 90/220/EEC ON THE DELIBERATE RELEASE INTO THE ENVIRONMENT OF GENETICALLY MODIFIED ORGANISMS (O.J. No. L117, 8/5/90 p. 15)

Article 16

1. Where a Member State has justifiable reasons to consider that a product which has been properly notified and has received written consent under this Directive constitutes a risk to human health or the environment, it may provisionally restrict or prohibit the use and/or sale of that product on its territory.
   It shall immediately inform the Commission and the other Member States of such action and give reasons for its decision.

2. A decision shall be taken on the matter within three months in accordance with the procedure laid down in Article 21.

Article 21

The Commission shall be assisted by a committee composed of the representatives of the Member States and chaired by the representative of the Commission.

The representative of the Commission shall submit to the committee a draft of the measures to be taken. The committee shall deliver its opinion on the draft within a time limit which the chairman may lay down according to the urgency of the matter. The opinion shall be delivered by the majority laid down in Article 148 (2) of the Treaty in the case of decisions which the Council is required to adopt on a proposal from the Commission. The votes of the representatives of the Member States within the committee shall be weighted in the manner set out in that Article. The chairman shall not vote.

The Commission shall adopt the measures envisaged if they are in accordance with the opinion of the committee.

If the measures envisaged are not in accordance with the opinion of the committee, or if no opinion is delivered, the Commission shall, without delay, submit to the Council a proposal relating to the measures to be taken. The Council shall act by a qualified majority.

If, on the expiry of a period of three months from the date of referral to the Council, the Council has not acted, the proposed measures shall be adopted by the Commission.