FOLKETINGET

Udvalget for Fødevarer, Landbrug og Fiskeri
(2. samling)
FLF alm. del - Bilag 251
Offentligt

**Udvalget for Fødevarer, Landbrug og Fiskeri**

**Til:** Udvalgets medlemmer og stedfortrædere
**Dato:** 30. april 2008

**Baggrundsmateriale til høringen om antibiotikaresistente genmarkører, onsdag den 7. maj 2008**

For god ordens skyld fremsendes hermed det endelige program for høringen om antibiotikaresistente genmarkører, der afholdes

**Onsdag den 7. maj 2008, kl. 9.30 i Landstingssalen på Christiansborg.**

Jeg vedlægger tillige en række baggrundsartikler og svar fra ministre til orientering.

Med venlig hilsen

Eva Esmarch,
Udvalgssekretær

## Program for høring om gmoér med antibiotikaresistente genmarkører, onsdag den 7. maj 2008

### Program

9.30 – 9.35 Indledning v/ formand for Fødevareudvalget **Jørn Dohrmann**

9.35 – 9.45 **Ilona Kryspin Sørensen,** *medlem af EFSA´s gmo panel (European Food Safety Authority) om betydningen af anvendelsen af gmoér med antibiotikaresistente genmarkører, baggrunden for gruppeopdelingen af antibiotikaresistens markørgener, behovet for en revurdering af denne klassificering. Risikovurdering af gmoér med antibiotikaresistente genmarkører.*

9.45 – 9.55 **Christian Friis**, medlem af Committee of Veterinary Medicinal Products i EMEA (European Medicines Agency) om betydningen af anvendelsen af gmoér med antibiotikaresistente genmarkører og risikovurdering og konsekvenser af anvendelsen af gmoér med antibiotikaresistente genmarkører.

9.55 – 10.05 **Jan Pedersen,** seniorforsker ved Fødevareinstituttet, DTU, om betydningen af anvendelsen af gmoér med antibiotikaresistente genmarkører og om dansk risikovurdering af gmoér med antibiotikaresistente genmarkører

10.05 – 10.15 **Niels Frimodt-Møller**, Statens Serum Institut, om betydningen af anvendelsen af gmoér med antibiotikaresistente genmarkører og om dansk risikovurdering af gmoér med antibiotikaresistente genmarkører

10.15 – 10.45 Spørgsmål/debat

10.45 – 11.15 Pause

11.15 – 11.25 **Dan Belusa**, Greenpeace om baggrunden for den fortsatte brug af gmoér med antibiotikaresistene genmarkører og muligheden for markedsføring af gmoér uden antibiotikaresistente genmarkører

11.25 – 11.35 **Kristofer Vamling,** BASF Plant Science's svenska dotterbolag Plant Science Sweden, om baggrunden for den fortsatte brug af gmoér med antibiotikaresistente genmarkører og om muligheden for markedsføring af gmoér uden antibiotikaresistente genmarkører

11.35 – 11.55 Spørgsmål/debat

11.55 – 12.00 Afslutning v/formand for Fødevareudvalget **Jørn Dohrmann**

## Baggrundsmateriale til høringen:

Opinion of the Scientific Panel on Genetically Modified Organisms on the use of antibiotic resistance genes as marker genes in genetically modified plants
*The EFSA Journal (2004) 48, 1-18*

Meddelelse fra Kommissionen om en fællesskabsstrategi mod antimikrobiel resistens
*Kommissionen for de Europæiske Fællesskaber, 20. juni 2001*

Committee for medicinal products for veterinary use and committee for medicinal products for human use
*Presence of the antibiotic resistance marker gene nptII in GM plants for food and feed uses*
*EMEA, 22 February 2007*

Statement of the Scientific Panel on Genetically Modified Organisms on the safe use of the nptII antibiotic resistance marker gene in genetically modified plants
*EFSA, 22-23 March 2007*

Svar på spm. 1 (alm.del. 2849 – landbrug og fiskeri) fra Folketingets Europaudvalg vedrørende antibiotikaresistente genmarkører i GMO'er, der også bruges i behandling.
*Ministeriet for Fødevarer, Landbrug og Fiskeri, 11. marts 2008*

Spørgsmål og svar på alm. del – spørgsmål nr. 157 - 158
*Ministeriet for Fødevarer, Landbrug og Fiskeri, 14. marts 2008*

Spørgsmål og svar på alm. del – spørgsmål nr. 159
*Ministeriet for Fødevarer, Landbrug og Fiskeri, 14. marts 2008*

Risikovurdering af GMO
*Jan Pedersen, Fødevareinstituttet, DTU*

Antibiotikaresistens-genmarkører i GMO'er – NPTII
*Niels Frimodt-Møller, Statens Serum Institut, april 2008*

Meddelelse fra Greenpeace med 15 punkter med kommentarer til emnet, april 2008.

*The EFSA Journal* (2004) 48, 1-18

# Opinion of the Scientific Panel on Genetically Modified Organisms on the use of antibiotic resistance genes as marker genes in genetically modified plants[1] (Question N° EFSA-Q-2003-109)

**Opinion adopted on 2 April 2004**


## SUMMARY

Directive 2001/18/EC (EC, 2001) states that Member States and the Commission shall ensure that GMOs which contain genes expressing resistance to antibiotics in use for medical or veterinary treatment are taken into particular consideration when carrying out an environmental risk assessment. This is with a view to identify and phase out antibiotic resistance marker genes (ARMGs) in GMOs which may have adverse effects on human health and the environment.

The Scientific Panel on genetically modified organisms (GMO Panel) of the European Food Safety Authority (EFSA) has evaluated the potential risks associated with specific ARMGs taking into account their current usage in clinical and veterinary medicine, the likely occurrence of horizontal gene transfer from genetically modified (GM) plants to microbes and the potential impact of horizontal gene transfer where naturally occurring resistance to the relevant antibiotics exists in the microbial gene pool. These factors will impact on the likelihood of any adverse effects on humans or the environment of ARMGs used in GM plants.

The GMO Panel considers the frequency of horizontal gene transfer from GM plants to other organisms as very low for all ARMGs considered. This, in itself, is an important consideration with regard to any risk posed by the use of ARMGs. However, with respect to clinical importance the Panel has categorised ARMGs into three groups with different potentials for compromising human health and the environment. ARMGs in the first group include genes conferring resistance to kanamycin and hygromycin. In this group the *nptII* gene, which confers kanamycin resistance, has a 13-year history of safe use in food crops and resistance to this group of antibiotics is widespread in naturally occurring microbes in humans and the environment. The Panel is of the opinion that with regard to safety there is no rationale for inhibiting or restricting the use of genes in this category, either for field experimentation or for the purpose of placing on the market. The second group of ARMGs, which includes resistance to chloramphenicol, ampicillin, streptomycin and spectinomycin, should be restricted to field trial purposes and should not be present in GM plants to be placed on the market. Given their current importance in clinical usage, the GMO Panel recommends that ARMGs placed in the third group, which includes those conferring resistance to amikacin and tetracyclines, are not present in GM plants to be placed on the market or in plants used for experimental field trials.


**Keywords:** Directive 2001/18/EC, GMOs, GM plants, antibiotics, antibiotic resistance marker genes, safety, human health, environment, horizontal gene transfer, *nptII* gene.

[1] For citation purposes: Opinion of the Scientific Panel on Genetically Modified Organisms on the use of antibiotic resistance genes as marker genes in genetically modified plants, *The EFSA Journal* (2004) 48, 1-18

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## BACKGROUND

Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms (EC, 2001) lays down in Annex III the information which may be necessary to carry out the environmental risk assessment. Article 4 (2) of the Directive states that Member States and the Commission shall ensure that GMOs which contain genes expressing resistance to antibiotics in use for medical or veterinary treatment are taken into particular consideration when carrying out an environmental risk assessment. This is with a view to identify and phase out antibiotic resistance marker genes (ARMGs) in GMOs which may have adverse effects on human health and the environment. This phasing out shall take place by the 31 December 2004 in the case of GMOs placed on the market according to Part C of the Directive and by 31 December 2008 in the case of GMOs authorised for experimental releases under Part B of the Directive. Annex II of Directive 2001/18/EC states that the risk assessment of the use of antibiotic resistance marker genes is a very specific issue and that further guidance may be recommended.

In accordance with Directive 2001/18/EC, a notification for placing on the market a GMO that has received a positive assessment report from a lead Member State is transmitted to the competent authorities of other Member States which can raise objections to the proposed marketing of the GMO during the statutory 60-day period and discuss outstanding issues for a further 45 days. Where objections are maintained, the Commission is required to consult the relevant Scientific Committees, now represented by the European Food Safety Authority (EFSA). The presence of ARMGs in the notified GMO products is often a reason for such objections.

The GMO Panel has recognised the need for guidance to notifiers, the Member States, and the Commission for identifying antibiotic resistance genes with the potential to be used as marker genes for GM plants and which may or may not have adverse effects on human health and the environment. The GMO Panel is aware of the limited availability of alternative marker genes for GM plants and of the ongoing development of marker removal systems. Future activities of the GMO Panel might focus on these alternatives in the event that more data become available.

## TERMS OF REFERENCE

Recognising the importance and urgency of the question, the GMO Panel has decided to task itself to deliver a scientific opinion on:

**antibiotic resistance genes with the potential to be used as marker genes for genetically modified plants and which may or may not have adverse effects on human health and the environment taking into account the limited availability of alternatives.**

The GMO Panel set up a Working Group on ARMGs to provide a scientific opinion in due time for the ongoing activity of the Working Group of Committee of the Competent Authorities under Directive 2001/18/EC on the implementation of Article 4 (2) of Directive 2001/18/EC.

## ASSESSMENT

### 1. Introduction

During the process of genetic modification of plants and other organisms, marker genes are normally used to facilitate the selection and identification of genetically modified cells, containing the gene of interest inserted into the genome of the host organism, among the vast majority of untransformed cells. This opinion deals solely with the use of antibiotic resistance marker genes (ARMGs) as particular concerns have been raised over the use of such genes and the potential for increased resistance to antibiotics in humans and animals as a result of horizontal gene transfer. The use of ARMGs has been common practice in microbial genetic research for many years and their utility has been extended successfully to the genetic modification of plants, including agricultural crops. ARMGs which may differ from those used to select the final transgenic plants are used in the initial molecular cloning procedures for construct development, an approach usually performed in micro-organisms. Since these genes can also be incorporated into the target plant the risk associated with the presence of these ARMGs needs to be considered alongside the ARMGs used specifically for the selection of successfully transformed cells.

GM plants approved for placing on the market and intended for unrestricted use by third parties might become widely distributed and used. A concern with respect to ARMGs is the theoretical possibility that the clinical therapy of orally administered antibiotics could be compromised through inactivation by antibiotic resistance proteins present in food derived from a GM plant containing an ARMG. The efficacy of antibiotic therapy is related to the topic of human and animal safety. Safety of ARMGs should be considered taking into account the following aspects: 1) prevalence of resistance to the antibiotic among bacteria in the intestine or in the environment and 2) the extent of use of the antibiotic and its importance for clinical human/animal therapy. Although there is no evidence that the presence of ARMGs in GM plants has caused any damage, it might be advisable to restrict the use of specific ARMGs. In this document, the key issues related to the biosafety of the use of ARMGs in GM plants are considered (reviewed by Bennett *et al.*, 2004).

### 2. Prevalence of antibiotic resistance genes in nature

Antibiotic resistance is a relatively common feature in natural microbial communities for a range of different habitats such as soils, aquatic systems and animal- and human-associated habitats. In fact, the majority of antibiotics currently used are produced in nature by micro-organisms (e.g. streptomycins are produced by streptomycetes), and the micro-organisms producing antibiotic themselves also contain the corresponding antibiotic resistance genes for

self-protection. The production of antibiotics is thought to represent a defence mechanism against competing micro-organisms, and is thus a key survival mechanism in nature. The mechanism(s) conferring antibiotic resistance in micro-organisms can vary, including options such as (1) enzymatic inactivation or modification of the antibiotic, (2) modification of host targets to prevent antibiotic binding, (3) failure of the antibiotic to be transported into and/or to be maintained in the micro-organism.

In addition to the presence of antibiotic resistance genes in the antibiotic-producer organisms, these genes also occur in natural bacterial assemblages in the so-called "horizontal gene pool", i.e. the fraction of genes in the bacterial population that is carried on mobile genetic elements such as plasmids and conjugative transposons. The horizontal gene pool provides flexibility to natural bacterial communities by protecting against the effect of antibiotics at times when antibiotic selective pressure is common in the local habitat.

During the last fifty years, antibiotic-resistant micro-organisms, in particular bacteria, have become prevalent in hospital- and/or patient-associated environments as a result of the ever-increasing use of antibiotics in clinical environments. Horizontal gene transfer and clonal selection are key genetic processes in these microbial populations. This scenario is true for each new antibiotic introduced. In addition, high prevalence of antibiotic resistance has been observed (in particular, tetracycline resistance) due to the use of antibiotics in agriculture, e.g. as feed additives. Resistance can persist in animal populations for a long period of time when the antibiotic is no longer used (Hinton *et al.*, 1986). A European survey of a range of habitats (including soils, waste water, and plant-associated habitats), performed under the EU research project RESERVOIR[2], showed that streptomycin, gentamycin and tetracycline resistances were widely spread in all environments tested, irrespective of whether the antibiotics were released into these environments (Heuer *et al.*, 2002; Van Overbeek *et al.*, 2002).

## 3. Antibiotic use and its effect on the antibiotic resistance gene pool

Pools of antibiotic resistance genes are thought to have been naturally present in microbial communities in natural and man-associated environments for a considerable period of time. The prevalence of these genes in natural microbial communities is strongly associated with the balance between the gain of fitness under selective pressure and the fitness loss under non-selective conditions. The outcome of this balance is unsure, often unpredictable and depends on the mechanisms involved. Rapid loss of antibiotic resistance from natural microbial communities has been observed in certain cases, e.g. for streptomycin resistance, but there are also examples of the persistence of the resistance trait, e.g. tetracycline resistance (Hinton *et al.*, 1986).

The increasing incidence of antibiotic resistance in microbial assemblages associated with environments important to humans and animals, in particular when present in the horizontal gene pool, poses an obvious risk to the ability of man to control pathogens in the clinical environment. This situation is difficult to solve, especially in the light of the potential persistance of antibiotic resistance in natural bacterial communities and the different mechanisms that can give rise to antibiotic resistance. In any case, prudent use of antibiotics will be the major strategy (Salyers, 1996).

## 4. The potential impact of horizontal gene transfer

The transfer of DNA, e.g. antibiotic resistance marker gene, from GM plant material to bacteria and the potential consequences are relevant issues to consider. Gene flow amongst bacteria is a

[2] BIO4-CT98-053, Antibiotic resistance genes in the environment: a comprehensive, multi-phasic survey of prevalence and transfer

well-established natural process that is recognised as central to their survival and evolution. This is especially well illustrated in the development of multiple drug resistance, a phenomenon that has been analysed in great detail and demonstrates the prominence of gene transfer and DNA rearrangement in bacteria. In contrast, there is no *a priori* reason to expect gene flow from plants to bacteria. Generally, it is accepted that the mechanism for such a transfer event would be the capture of DNA released from GM plant material by competent bacteria via natural transformation.

Thus, an important factor may be the persistence of plant-derived DNA in the environment during crop cultivation and harvesting (and in soil residues), during food processing and in the human or animal gastro-intestinal tract. GM plant material intended for use in food is often subject to a variety of processing regimes. These range from simple heat treatment (e.g. canning) to the extraction of food ingredients. Food processing and extraction of ingredients may physically damage, degrade or remove DNA and this limits gene transfer. Published studies on the susceptibility of DNA to processing and extraction regimes have been reviewed (Klein *et al.*. 1998). The gastro-intestinal tracts of man and animals degrade DNA and destroy intact biologically active genes (Beever and Kemp 2000). However the process of inactivation is not complete, especially in the more proximal regions of the gastro-intestinal tract.

Experimental studies on the fate of DNA involve detection using PCR amplification and the assessment of biological activity/integrity of DNA by transformation studies. Mercer *et al.* (1999; 2001) investigated DNA degradation in the human oral cavity and demonstrated that although DNA was rapidly degraded, sufficient biological activity remained to allow transformation of competent *Streptococcus gordonii* cells. Duggan *et al.* (2000) investigated sheep saliva and rumen fluid, concluding that DNA remained available for transformation in the oral cavity but was rapidly inactivated further down the gastro-intestinal tract. Duggan *et al.* (2003) investigated maize grains and found that the cellular matrix protected DNA from degradation. Martin-Orue *et al.* (2002) found that DNA in food was degraded much slower than pure DNA. Chambers *et al.* (2002) used chicken feeding experiments to explore the *in vivo* fate of the bacterial ampicillin resistance gene *bla* in bacteria and transgenic maize. The gene was found in the stomach contents when GM maize was fed to chickens but not in the lower intestine. In contrast, feeding bacteria containing *bla* led to the detection of the gene throughout the intestinal tract. Netherwood *et al.* (2002) used human ileostomists to monitor the survival of transgenes in GM plant material during passage through the human gastro-intestinal tract. Transgene survival was detected in the small intestine but in a trial using human volunteers with an intact gastro-intestinal tract no transgenic DNA was detected in their faeces.

Various experiments (Schubbert *et al.*, 1994; 1997; 1998; Hohlweg and Doerfler, 2001; Klotz and Einspanier, 1998; Einspanier *et al.*, 2001) have demonstrated that pure DNA as well as plant-associated DNA, when consumed in a diet, can sometimes be detected in very low amounts in blood and tissues. There is no reason to expect differences in the fate of DNA derived from GM plants and non-GM plants. It is very well established that some bacterial species possess highly evolved processes that allow them to take up DNA from the environment (Lorenz and Wackernagel, 1994). However, the development of this 'competence' is a regulated process that depends on particular environmental circumstances. Bacteria produce restriction endonucleases that degrade incoming foreign DNA and, to be maintained, DNA that is not degraded must be capable of replication. This depends either on the presence of a genetically linked replicon or an integration event. In characterised natural transformation systems (Chen and Dubnau, 2003) DNA is taken into the cell as a single strand. Efficient integration depends on DNA homology between incoming DNA and the recipient bacterial genome (Lewin, 2000) or on a site-directed integration mechanism, the latter being highly specific. Integration can also involve a rare 'illegitimate' recombination event. Thus, the provision of DNA homology between the transgene and the recipient bacterial genome will facilitate plant to bacterium DNA transfer (Gebhart and Smalla, 1998; Nielsen *et al.*, 1998, 2000). The DNA acquired by the bacterium is unlikely to be of significance unless it is expressed or alters the expression of resident genes.

Bacterial gene expression depends on specific genetic signals that are not universal between species providing another molecular barrier.

DNA transfer from GM plant material to micro-organisms has been investigated in a limited number of experimental studies. Schluter *et al.* (1995) used *Erwinia chrysanthemi* as a recipient in experiments with transgenic potato. The latter carried a complete copy of a bacterial plasmid capable of replication and marker gene expression in *Erwinia*. This pathogen lyses plant tissues with extracellular pectinolytic enzymes and thus has an intimate association with the plant material. Despite this, evidence for plant to bacterium transfer was not found. Gebhard and Smalla (1998) and de Vries and Wackernagel (1998) used naturally competent *Acinetobacter* to investigate plant to bacterium gene transfer by marker rescue. This process depends on the presence of DNA homology between the transgene and recipient bacterium and transformation involves the correction of a mutation by homologous recombination. In all cases, the plant material carried an *npt*II kanamycin resistance gene and the recipient bacteria carried an inactivated homologue of the same gene but controlled by a bacterial promoter. Transformants could only be detected when the *npt*II gene in the bacteria was restored. When the DNA homology between donor and recipient was removed, transformation fell below the limit of detection, suggesting the absence of adventitious degrees of homology between the integration and the recipient genome (Nielsen *et al.*, 1998). Thus, whilst there is evidence for gene transfer by marker rescue, the recovery of unique DNA from the transgenic plant was not demonstrated. There is a similar report of marker rescue using GM potatoes with *Acinetobacter* and *Pseudomonas stutzeri* (De Vries *et al.*, 2001). Nielsen *et al.*. (2000) extended the findings on marker rescue to soil and Kay *et al.* (2002) included studies in GM plants in which transgenic DNA was integrated within the chloroplast genome.

Thus, horizontal gene transfer from plants to micro-organisms is possible, but with a low frequency when enforced under specific experimental conditions conducive to the gene transfer process (e.g. the presence of homology between sequences flanking the transgenic DNA and the genome of the recipient bacterium). The frequency is apparently very low under natural circumstances (Nielsen *et al.*, 2000; Kay *et al.*, 2001). A current EU sponsored project TRANSBAC[3] attempts to map the occurrence of anchor sequences across plant and bacterial genomes.

## 5. Antibiotic resistance genes with marker function in plants

### 5.1. Kanamycin resistance: *npt*II gene

The *npt*II [= aph(3´)-IIa] gene is widely used as a selectable marker (often referred to as kanamycin resistance gene or neomycin resistance gene) in the transformation of organisms as diverse as bacteria, yeasts, plants and animals. It was the first marker used in plant genetic transformation and is still the most commonly used marker in the selection of transformed plants. Kanamycin is normally used as the selective agent for the *npt*II gene.

*Origin* - The gene originates from the transposon Tn5 of *Escherichia coli* K12 (Garfinkel *et al.*, 1981).

*Catalytic activity and substrate specificity* - The gene encodes neomycin phosphotransferase. Neomycin phosphotransferase is a type II aminoglycoside-3'-phosphotransferase (APH (3')II) catalyzing an ATP-dependent phosphorylation of the 3'-hydroxyl group of the aminohexose moiety of certain aminoglycoside antibiotics (Bryan, 1984). The modified kanamycin molecule can no longer bind to the 30S ribosomal subunit to cause misreading of mRNA and thus inhibit

[3] QLK3-2001-02242, Gene flow from transgenic plants: evaluation and biotechnology.

protein synthesis. Since the phosphorylation is ATP-dependent, ATP has to be present in sufficient amounts for the catalytic reaction to take place. The APH(3')II protein has the antibiotics kanamycin, neomycin, paromomycin, ribostamycin, butirosin, gentamicin B and geneticin (G418) as substrates and renders the carrier of the trait resistant to these antibiotics. Resistance has not been conferred for amikacin, but enzymatic activity for this substrate is detectable *in vitro*. The marker gene commonly used in genetic modifications of plants encodes an aminoglycoside 3'-phosphotransferase that confers resistance only to the antibiotics neomycin, kanamycin and geneticin (as reviewed by Redenbaugh *et al.*, 1993, 1994). Mutations in the *npt*II gene may result in modifications of the amino acid sequence of the protein that may eliminate, reduce or increase aminoglycoside resistance or lead to an alteration in the substrate specificity of the enzyme. For instance, a point mutation in the *npt*II gene modified the specificity of the enzyme conferring the ability to phosphorylate amikacin (Kocabiyik and Perlin 1992). However, no amikacin resistant strains with clinical significance have been obtained so far by introducing a single mutation in the *npt*II gene. Resistance which is clinically significant could only be obtained under laboratory conditions and required two simultaneous and rare mutation events affecting two different genes, *npt*II and a gene encoding a permease (Perlin and Lerner, 1996). The natural occurrence of such double mutants has not been reported, while resistance to gentamycin, amikacin and tobramycin caused by the presence of a number of other antibiotic resistance genes is widespread (Schmitz *et al.*, 1999).

***Therapeutic importance of the relevant antibiotics** (kanamycin, neomycin, geneticin)* – Kanamycin is rarely used today because of its considerable side effects. Only under conditions of multiple mycobacterial resistance to other drugs is kanamycin still used as a reserve tuberculostatic agent. For the same reason as kanamycin, neomycin, which is poorly absorbed orally, is also rarely used intravenously/intramuscularly to treat infections. Neomycin is sometimes used orally for pre-operative bowel sterilization, for selective gut decontamination in certain high-risk patients, or for the treatment of hepatic encephalopathy. Kanamycin and neomycin are also components in some formulations used for localised treatments of infections in skin, eyes and ears. These antibiotics are rarely administered orally, which minimizes the selective pressure for antibiotic resistance in the gut. Their use in the treatment of humans has been superceeded by more effective aminoglycoside antibiotics that are not substrates for APH(3')-II (Nap *et al.*, 1992). However, neomycin has some veterinary use, primarily to treat calves and pigs (and poultry) for intestinal infections (enteritis). It is also used for the treatment of bacterial skin infections, including dermatitis and eczema in cats and dogs. The antibiotics are rarely used in agriculture or aquaculture and thereby do not provide selective pressure for a possible transfer of the resistance genes from genetically modified plants to soil micro-organisms. In contrast to kanamycin and neomycin, geneticin is only used for *in vitro* experimentation e.g. as a selective agent for eukaryotic GM cells.

***Resistance occurrence*** – Kanamycin as well as neomycin resistant bacteria are ubiquitous in nature. Selective plating of soil bacteria on kanamycin-containing medium can reduce the microbial count from $10^7$ to $10^4$ CFU/g (Smalla *et al.*, 1993; Smalla and van Elsas 1996). However, only a fraction of kanamycin resistant bacteria often contain the *aph*(3')-IIa gene. The other resistant bacteria have other genes conferring kanamycin resistance. At least seven isozymes of APH (3´) have been reported in the literature. The *aph*(3')-IIa gene which encodes the APH (3´)-IIa protein has been reported to occur naturally only in eubacteria. The gene occurs in gram-negative organisms and *Pseudomonas* spp. In one survey, three out of 350 kanamycin resistant bacterial isolates from different soils, river water, sewage and pig slurry contained *aph*(3')-IIa sequences (Smalla *et al.*, 1993). The organisms belonged to the Proteobacteria, being classed as *Aeromonas* spp. and *Escherichia coli*. Leff *et al.* (1993) showed similar data (3/184 positives) for stream isolates. In a survey of over 4200 clinical isolates resistant to one or more aminoglycoside antibiotics, 2.5% of the bacteria contained the *aph*(3')-IIa sequences. The data emphasise that, although there is a great diversity of genes encoding aminoglycoside-modifying enzymes, most of these genes are currently restricted to gram-negative bacteria. This phenomenon may be due to different requirements for gene expression, plasmid replication,

and barriers of genetic exchange. Aminoglycoside resistant bacterial strains often emerge as a result of acquiring plasmid-borne genes encoding aminoglycoside-modifying enzymes (Courvalin and Carlier 1981). Furthermore, many of these genes are associated with transposons, which aid the rapid dissemination of drug resistance. Using worst case probability estimates for hypothetical gene transfer, it has been concluded that the additive effect of an *aph*(3')-IIa gene-containing DNA fragment entering the human gastrointestinal flora from genetically engineered plants is insignificant in terms of gaining a selective advantage when compared to the population of kanamycin resistant micro-organisms naturally present.

*Other safety considerations* - The purified enzyme has been shown to be rapidly degraded in studies simulating normal gastric and intestinal conditions (Fuchs *et al.*, 1993a, b); the protein degraded in 10 seconds and no enzymatic activity was found after 5 min. Thus, in the stomach and small intestine, most, if not all, APH (3')II protein will be inactivated or degraded by the acidic environment and digestive enzymes. Under simulated abnormal conditions in neutralized gastric fluid (which may exist in patients treated with drugs that reduce stomach acidity) the enzyme may remain active. Even if not degraded, APH (3')II would not function under the limited concentration of ATP present. Using GM tomato expressing the APH (3')II marker protein as an example, and assuming that the tomato was eaten together with 1 g of relevant antibiotic (neomycin), loss of antibiotic efficacy would be maximally only 1.5% (Redenbaugh *et al.*, 1993, 1994). The number is based on the following assumptions: 1) 95th percentile consumption[4], at a single serving, of specific fruits or vegetables high in ATP content; 2) calculations based on a survey of a three-day consumption period; 3) stoichiometric reaction of 100% of the ATP in ingested food with orally administered neomycin; 4) administration of neomycin simultaneously with consumption of a GM food containing APH(3')-II and other fruits or vegetables rich in ATP; 5) presence of intact, functional APH(3')-II enzyme, which requires a buffered stomach environment (pH 7); and 6) stability of ATP in the stomach environment. The conclusion was that there is no risk of compromising efficacy of oral therapeutic use of kanamycin and neomycin due to APH(3')-II present in food (Redenbaugh *et al.*, 1993, 1994).

## 5.2. Hygromycin resistance: *hph* gene

*Origin* - The *hph* [= *aph*(4)Ia] gene originates from *Escherichia coli* W677 carrying the plasmid pJR225. Two major genes encoding Hph protein have been characterized. The first gene was isolated from *Streptomyces hygroscopicus* (Leboul and Davies, 1982; Malpartida *et al.*, 1983), a hygromycin B producing species. The second gene is a plasmid-borne resistance gene isolated from *Escherichia coli* (Rao *et al.*, 1983; Kuhstoss and Rao, 1983) and *Klebsiella pneumoniae* (Gritz and Davis, 1983). Most vectors containing resistance genes and used in gene transfer experiments with plants harbour the *E. coli hph* gene.

*Catalytic activity and substrate specificity* - The *hph* gene encodes hygromycin phosphotransferase (Waldron *et al.*, 1985). The protein of this gene inactivates, specifically, the antibiotic hygromycin B by phosphorylation (Gritz and Davies, 1983). Other aminoglycoside aminocyclitol antibiotics such as kanamycin or geneticin are not substrates for the enzyme. The *hph* gene is 1023 bp and rich in CpG dinucleotides (103 CpG). To avoid any *hph* gene silencing in eukaryotic expression vectors due to the high proportion of CpG dinucleotides, a functional synthetic *hph* gene is available. In the synthetic gene all of the CpG motifs have been removed and the codon usage optimised. The synthetic *hph*-DCpG gene displays higher hygromycin resistance than its wild-type counterpart.

*Therapeutic importance* – Hygromycin is not in human clinical use but may be used in veterinary medicine for treatment of swine and poultry (USA, not licensed in the UK).

[4] Confidence interval, in which the true mean value can be found with a likelyhood of 95%

***Resistance occurrence*** – No systematically published information available.

### 5.3. Streptomycin resistance: *aadA* (Strep/Spec$^R$) gene

***Origin*** – The *aadA* [= *ant*(3")-Ia, Strep/Spec$^R$] gene originates from the plasmid R538-1 of *Escherichia coli.* The gene is ubiquitous among gram-negative bacteria and has been cloned from several transposons. Tomalsky and Crosa (1987) detected the aadA (Strep/Spec$^R$) gene on the multiresistance transposon Tn1331 in *Klebsiella pneumonia*.

***Catalytic activity and substrate specificity*** – The gene encodes streptomycin adenyltransferase (Davies and Smith, 1978) which modifies the position of hydroxyls in the ring structures of streptomycin and spectinomycin.

***Therapeutic importance*** – Streptomycin is vestibulotoxic and cochleotoxic and has mostly been replaced by newer aminoglycosides. However, it is still sometimes used for specific purposes e.g., treatment of gonorrhea. Tuberculosis and brucellosis, and in combination with a beta-lactam agent or a glycopeptide for treating enterococcal endocarditis with high-level gentamicin (but not streptomycin) resistance. Streptomycin is also used as a pesticide in agriculture, although the known use is concentrated in the USA and Japan and is sparse in Europe.

***Resistance occurrence*** – The *aadA* gene has been found in association with several transposons (Tn7, Tn21 etc.). Extrachromosomal elements (plasmids) carrying streptomycin resistance genes are common and can be found at high frequency in natural populations of bacteria (Shaw *et al.*, 1993) and in clinical isolates (Heym *et al.*, 1994). They are ubiquitous especially among gram-negative bacteria. In one study, 58.7% of the surveyed strains were shown to be streptomycin resistant and of these 55.5% carried the *ant*(3")-Ia gene. Use of streptomycin or spectinomycin as a pesticide provides selective pressure in the environment, and will select for streptomycin resistant (plant-associated) bacteria. There are several recorded instances of such bacterial isolates (mostly obtained from apple orchards) in which streptomycin had been applied as a pesticide.

### 5.4. Ampicillin resistance: amp$^r$ gene

***Origin*** - The plasmid R7268, with its transposon Tn3 and the β-lactamase gene (*amp$^r$*, *bla*$_{(TEM-1)}$) was originally isolated from a hospital bacterium isolate [patient Thomas Edison Murphy (= TEM)] in 1963. A typical molecular cloning vector used for genetic engineering has a pBR322- or pUC-derived backbone. Such vectors contain the *bla* $_{(TEM-1)}$ gene of RSF 2124 plasmid.

***Catalytic activity and substrate specificity*** - The *amp$^r$* gene encodes TEM-1 β-lactamase (Sanders and Sanders, 1992) which hydrolyses the amide bond in the beta-lactam ring of the antibiotic ampicillin. Substrates for the β-lactamase are ampicillin, penicillin G and amoxycillin. The TEM-1 enzyme has only a minor activity against recent cephalosporines and can be inhibited by β-lactamase inhibitors such as clavulanic acid or tazobactam. However, in the case of *E. coli*, a high expression rate of the β-lactamase may render the bacteria resistant to amoxicillin/tazobactam and other combinations of β-lactams with β-lactamase inhibitors (Sanders and Sanders, 1992). Moreover, mutations in the β-lactamase (e. g. TEM-30 to TEM-41) may result in reduced clavulanic-acid inhibition. In the classification scheme by Bush *et al.* (1995), such variants were introduced as a subclass of its own, 2br. So far, these inhibitor-resistant TEM β-lactamases (IRTs) have only been found in *E. coli* and sporadically in *Proteus mirabilis* or *Klebsiella* (Bermudes *et al.*, 1997).

***Therapeutic importance*** – Ampicillin is an important antibiotic for humans as well as animals. In many cases, e.g. in the treatment of urinary tract infections, the use of ampicillin/amoxicillin is

recommended only when ampicillin/amoxicillin sensitivity has been proven. However, it is widely used to treat respiratory tract infections in humans. In the case of certain infections, e.g. with enterococci or *Listeria monocytogenes*, ampicillin is still considered to be the drug of choice. In veterinary medicine, ampicillin is used for treatment of bacterial infections in cattle, pigs and sheep and of mastitis in cattle. Amoxycillin is used for treatment of bacterial infections in cats and dogs, and respiratory and urogenital tract infections in cattle, pigs and sheep.

***Resistance occurrence*** – There is a significant background of ampicillin-resistant bacteria in the normal human intestine. Of healthy humans, 19% harboured ampicillin-resistant *E. coli* in their intestine (DANMAP, 1997). Between 30 and 40% of Finns carry ampicillin-resistant coliform bacteria (Leistevuo *et al.*, 1996). Because about 80% of these bacteria are *E. coli*, in which the most common resistance genes are of the TEM family, it is probable that about one third of Finns carry a TEM-1-containing bacterium. Also about 35% of *E. coli* isolates from clinical environments exhibit ampicillin resistance (Kresken *et al.*, 1999; DANMAP, 2001). Around 90% of these cases are due to the β-lactamase type TEM 1 (Livermore, 1995). The corresponding gene is also widespread in other enterobacterial species as well as in *Haemophilus sp.*, *Neisseria gonorrhoeae* and *Salmonella sp.*. The TEM-1 gene is common also in bacteria of animal origin. Danish data show that the prevalence of ampicillin resistant *E. coli* in broilers, cattle and pigs are 16, 0, and 10%, respectively (DANMAP, 2001). In clinical isolates, however, the occurrence of ampicillin resistance can be as high as 80% in cattle (DANMAP, 2001). During ampicillin therapy, the number of resistant bacteria increases because of their selective advantage in the intestine. Due to the extremely low probability of transfer of the resistance gene from genetically modified plants to intestinal bacteria, occurrence of such events would not add significantly to the existing background of ampicillin-resistant bacteria in the intestine.

### 5.5. Kanamycin resistance: *npt*III gene

***Origin*** - The *npt*III [= *aph*AIII, *aph*(3')IIIa] gene originates from *Enterococcus faecalis* R plasmid.

***Catalytic activity and substrate specificity*** – The gene encodes a type III aminoglycoside-3' phosphotransferase [APH(3')III] that is characterized by resistance to kanamycin, neomycin, paromomycin, ribostamycin, lividomycin, butirosin and gentamicin B (Shaw *et al.*, 1993). Amikacin and isepamicin are also modified *in vitro*, although many strains express only a low level of resistance.

***Therapeutic Importance*** – Amikacin is a reserve antibiotic of significant value in the treatment of nosocomial infections involving Gram-negative organisms resistant to gentamicin and tobramicin.

***Resistance occurrence*** – No systematically published information available.

### 5.6. Chloramphenicol resistance: $Cm^R$ gene

***Origin*** - The $cm^R$ (= *cat)* gene originates from the transposon Tn9.

***Catalytic activity and substrate specificity*** - The gene encodes chloramphenicol acetyltransferase (CAT) which catalyzes an acetyl-CoA-dependent acetylation of the antibiotic chloramphenicol, and thus, abolishes its antibacterial effect (Proctor and Rownd, 1982).

***Therapeutic Importance*** – Chloramphenicol is a broad-spectrum antibiotic. Its serious side-effect (aplastic anemia), although uncommon, restricts its systemic use in the developed world, where it is mainly used for topical treatment of eye, ear and skin infections in human and veterinary medicine. It is still used widely in developing countries. In humans, chloramphenicol is a first choice antibiotic for purulent meningitis of unknown etiology in patients who are highly allergic

to beta-lactam agents. Chloramphenicol is also an alternative for serious infections caused by bacteria resistant to other antibiotics. In veterinary medicine, chloramphenicol can be used for the treatment of serious infections in non-food-producing animals but is not authorised in the EU for use in food-producing animals.

*Resistance occurrence* – Resistant micro-organisms are widely found in the environment.

### 5.7. Tetracycline resistance: tetA gene

*Origin* - The *tet*A gene originates from the transposon Tn10.

*Catalytic activity and substrate specificity* - The gene encodes a membrane protein which causes the efflux of tetracyclines (Bryan, 1984). Tetracyclines are chemically closely related to one another, all being derivatives of naphthacene structure.

*Therapeutic Importance* – Tetracycline and its derivatives are broad-spectrum antibiotics that have been extensively used in both human and veterinary medicine over more than 50 years for the treatment of a variety of infections. They are still used for treating infectious diseases due to organisms such as *Brucella, Chlamydia, Mycoplasma, Rickettsia and Vibrio* spp. etc and in the treatment of acne. However, due to widespread resistance their usefulness is now considerably more limited than earlier.

*Resistance occurrence* – The *tet* genes are widespread in the environment. The European project RESERVOIR in its final report (1999) records several instances of the widespread occurrence of diverse tet genes, as evidenced by molecular means.

## 6. Classification of antibiotic resistance genes by their biological distribution and based on the present state of therapeutic importance of the relevant antibiotics

If the transfer of an antibiotic resistance gene from the genome of a transgenic plant to that of a bacterium should occur at all, the risk associated with this very rare event should be viewed against the presence of antibiotic resistance genes in soil, plant, water and enteric bacteria. Furthermore, consideration must be given to the importance of specific antibiotics in therapeutic use. On the basis of these two criteria for evaluation, the above-mentioned antibiotic resistance genes useful as markers in genetic modification of plants have been assigned to three groups:

### 6.1. Group I

Group I contains antibiotic resistance genes which (a) are already widely distributed among soil and enteric bacteria and (b) confer resistance to antibiotics which have no or only minor therapeutic relevance in human medicine and only restricted use in defined areas of veterinary medicine. It is therefore extremely unlikely (if at all) that the presence of these antibiotic resistance genes in the genome of transgenic plants will change the already existing bulk spread of these antibiotic resistance genes in the environment or will impact significantly on human and animal health. This refers to the following two antibiotic resistance genes.

- *npt*II gene: The substrates of the APH(3´)II enzymes include the antibiotics, kanamycin, neomycin, paromycin, butirosin, gentamicin B and geneticin (G 418). The antibiotics of this category which are relevant for human therapy, amikacin, gentamicin (predominantly $C_1$, $C_{1a}$ and $C_2$) and other aminoglycosides and aminocyclitoles, are not substrates for the APH(3´)-II enzymes. The *npt*II gene is widely spread in micro-organisms in the environment (Smalla *et al.*, 1993; Leff *et al.*, 1993).

- ***hph* gene:** Hygromycin is not used in human therapy, and there is no cross-resistance with other antibiotics used for human therapy. The antibiotic was originally developed for veterinary use and is still added in some parts of the world to animal feed as an anthelmintic.

### 6.2. Group II

Group II contains antibiotic resistance genes which (a) are widely distributed in micro-organisms in the environment (soil, plant, water and the mammal gut) and (b) confer resistance to antibiotics which are used for therapy in defined areas of human and veterinary medicine. The presence of these antibiotic resistance genes in the genome of transgenic plants will have only a minimal effect on the bulk spread of these antibiotic resistance genes in the environment, and therefore will have a minimal impact on human and animal health, if at all. Their presence in genetically modified plants will thus not contribute to their occurrence in bacteria. This refers to the following antibiotic resistance genes.

- ***Cm*$^R$ gene:** Chloramphenicol-resistant micro-organisms are widely distributed in the environment, and many of these carry the *Cm*R gene. In the EU, chloramphenicol is rarely used for medical purposes because of the risk of causing aplastic anaemia and has not been authorized for use in food-producing animals.
- ***ampr* gene:** It is reasonable to assume that almost every person on earth harbours or has harboured *Escherichia coli* cells containing the ampr gene in their intestinal tract, even without exposure to β-lactam antibiotics. This is supported by the observation that approximately 35 % of all clinical *E. coli* isolates are resistant to ampicillin (Kresken *et al.*, 1999) of which 90%, in turn, are caused by TEM-1 β-lactamases (Livermore, 1995). Studies (BgVV, 1997) have also demonstrated that approximately 74 % of all *E. coli* isolates from cattle and swine are ampicillin resistant. Thus, even in the light of the clinical relevance of ampicillin, the presence of *amp*R (bla gene) in transgenes is not seen to siginificantly alter the existing pool of already resistant bacteria.
- ***aadA gene*:** Streptomycin and spectinomycin are used in human medicine to a limited extent only (WHO, 1993). However, they still are of importance in human medicine for the treatment of tuberculosis (streptomycin) or gonorrhoea (spectinomycin). *Aad*A is to a limited extent prevalent in a range of environmental habitats (Van Overbeek *et al.*, 2002).

### 6.3. Group III

Group III contains antibiotic resistance genes which confer resistance to antibiotics highly relevant for human therapy and, irrespective of considerations about the realistic value of the threat, should be avoided in the genome of transgenic plants to ensure the highest standard of preventive health care. This refers to the following antibiotic resistance genes.

- ***npt*III gene:** For use in human therapy, amikacin is an important reserve antibiotic whose therapeutic importance should not, even potentially, be reduced by the use of the *npt*III gene in the establishment of genetically modified plants.
- ***tet*A gene:** Tetracyclines are characterized by their wide spectrum of action and continue to be of therapeutic importance in human medicine; they are used to control *Brucella*, *Chlamydia*, *Mycoplasma*, *Rickettsia*, *Vibrio*, etc.

## CONCLUSIONS AND RECOMMENDATIONS

With regard to current scientific and technical knowledge, ARMGs are still required in the majority of cases to ensure the efficient selection of transgenic events in plants. Also based on

present scientific knowledge, gene transfer from GM plants to bacteria under natural conditions cannot be excluded but it would be a very unlikely event. Therefore, such a rare event will not contribute effectively to the extant abundance of antibiotic resistance marker genes in bacteria in the environment (soil, plants, water and human and animal guts).

Directive 2001/18/EC states that the future development of genetically modified plants to be placed on the market and to be used in the production of food or feed should aim at avoiding genes which confer resistance to therapeutically relevant groups of antibiotics. With regard to this requirement the GMO Panel considered (1) the biosafety of using ARMGs in GM plants, (2) the extant pool of antibiotic resistance genes in natural bacteria and (3) best practices for the future use of ARMGs in GM plants.

The GMO Panel concludes that:

1. The frequency of horizontal gene transfer from GM plants to other organisms is very low for all three groups of ARMGs considered. This in itself is an important consideration with regard to the risk posed by the use of ARMGs.
2. For all of the antibiotics and resistances considered, it has been shown or is extremely likely that there is a considerable extant pool of resistance genes already present in the microbiota in the environment.
3. With regard to best practice, the requirements of Directive 2001/18/EC regarding therapeutically important antibiotics and the desire to limit the use of ARMGs, the Panel considers that ARMGs placed in group I (e.g the *npt*II marker) have a 13-year history of safe use in food crops. Furthermore, resistance to antibiotics in group I is widespread in naturally occuring prokaryotic gene pools. This, together with the other reasons provided in this document, indicates that there is no rationale for restricting or prohibiting the use of this group of ARMGs.

The use of ARMGs in group II should be restricted to field trial purposes and should not be present in GM plants to be placed on the market. Experimental releases of GM plants (according to part B of Directive 2001/18/EC) are generally confined, being limited in time and space. GM plants in experimental releases are not intended for use in foods or feeds. No hazardous effects on human health and the environment are thus to be expected from the presence of the ARMGs in GM plants used for experimental releases under approved conditions.

Given their current importance in clinical usage, the GMO Panel recommends that ARMGs placed in group III are not present in GM plants to be placed on the market or in plants used for experimental field trials (according to part B of Directive 2001/18/EC).

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KOMMISSIONEN FOR DE EUROPÆISKE FÆLLESSKABER

Bruxelles, den 20.06.2001
KOM(2001) 333 endelig

BIND I

# MEDDELELSE FRA KOMMISSIONEN

# OM EN FÆLLESSKABSSTRATEGI MOD ANTIMIKROBIEL RESISTENS

# RESUMÉ

Forekomsten og udbredelsen af antimikrobiel resistens er blevet et alvorligt problem for folkesundheden i Fællesskabet og på verdensplan. Overforbrug og misbrug af stoffer, som standser eller hæmmer væksten af mikroorganismer (herunder bakterier, vira og svampe) og visse parasitter (f.eks. protozoer) har muliggjort en øget forekomst af resistente organismer. Den såkaldte "antimikrobielle resistens" kan spredes til andre mikrobielle populationer. Infektionen med resistente organismer truer mennesker, dyr og planter, herunder også dem, som ikke tidligere har været i kontakt med antimikrobielle agenser.

I forbindelse med meddelelsen forstås ved "antimikrobiel agens" et stof, som enten produceres syntetisk eller naturligt af bakterier, svampe eller planter, og som anvendes til at standse eller hæmme væksten af mikroorganismer, herunder bakterier, vira og svampe, samt parasitter, som er resistente (navnlig protozoer). Antibiotika er stoffer med en antibakteriel virkning.

I videnskabelige udtalelser, som er blevet fremsat for nylig, understreger man, at der er behov for en hurtig reaktion inden for følgende områder: forsigtig anvendelse af antimikrobielle agenser, forebyggelse af sygdomme, udvikling af nye produkter og behandlingsmetoder samt overvågning af situationen.

Antimikrobiel resistens behandles allerede af Fællesskabet ved hjælp af forskellige individuelle foranstaltninger. Der er et klart behov for en overordnet tilgangsvinkel til spørgsmålet, som er baseret på artikel 152 i traktaten om oprettelse af Det Europæiske Fællesskab, som bestemmer, at der skal sikres et højt sundhedsbeskyttelsesniveau ved fastlæggelsen og gennemførelsen af alle Fællesskabets politikker og aktiviteter.

På dette grundlag foreslår Kommissionen, at der fastlægges en fællesskabsstrategi for fire centrale indsatsområder:

(1) **Overvågning:** Overvågning af udviklingen og effekten af de forskellige indgreb gennem oprettelsen/styrkelsen af effektive overvågningssystemer vedrørende antimikrobiel resistens hos mennesker og dyr samt forbruget af antimikrobielle agenser.

(2) **Forebyggelse** af overførbare sygdomme og infektionskontrol med henblik på at mindske behovet for antimikrobielle agenser. Det omfatter forsigtig anvendelse af antimikrobielle agenser, hvilket medfører et behov for forbedret produktinformation vedrørende antibakterielle lægemidler og fremme af foranstaltninger vedrørende uddannelse og adfærd, som er rettet mod fagfolk og offentligheden.

(3) **Forskning og produktudvikling:** Nye metoder til forebyggelse og behandling af infektioner samt fortsat støtte til forskning vedrørende nye lægemidler og alternative behandlingsmuligheder.

(4) **Internationalt samarbejde:** Antimikrobiel resistens respekterer ikke landegrænserne. En effektiv strategi kræver tæt samarbejde og høringer med deltagelse af Kommissionen, medlemsstaterne og andre involverede parter, navnlig på internationalt plan.

Det vedlagte forslag til Rådets henstilling om forsigtig anvendelse af antimikrobielle agenser spiller en vigtig rolle i Fællesskabets tværfaglige og mangesidede tilgangsvinkel.

# MEDDELELSE FRA KOMMISSIONEN

# OM EN FÆLLESSKABSSTRATEGI MOD ANTIMIKROBIEL RESISTENS

**(EØS-relevant tekst)**

# INDHOLDSFORTEGNELSE

# INDLEDNING

## Baggrund

Opdagelsen, udviklingen og tilgængeligheden af stoffer, som stopper eller begrænser væksten af mikroorganismer (bakterier, vira og svampe) og parasitter (f.eks. protozoer) har revolutioneret behandlingen af infektionssygdomme, hvilket har ført til en dramatisk nedgang i sygeligheden og dødeligheden. Sådanne "antimikrobielle agenser" (som i forbindelse med meddelelsen omfatter stoffer, som enten produceres syntetisk eller naturligt af bakterier, svampe eller planter, og som anvendes til at standse eller hæmme væksten af mikroorganismer, herunder bakterier, vira og svampe, samt parasitter, som er resistente, navnlig protozoer) har i høj grad bidraget til forbedringer af folkesundheden. Antibiotika er stoffer med en antibakteriel virkning.

Sygdomsfremkaldende organismer har dog en påfaldende evne til at tilpasse sig, herunder især til at udvikle og overføre antimikrobiel resistens. Derudover fremmer overdreven og ukontrolleret brug af antimikrobielle agenser væksten af resistente organismer og bringer således tidligere årtiers landvindinger i fare. Selv om antimikrobiel resistens fra naturlige kilder også fandtes før antimikrobielle agenser blev indført i den medicinske behandling, er det den generelle holdning, at der er en forbindelse mellem de mængder, som anvendes, og den øgede forekomst af resistente organismer.

På trods af den nuværende forskning med henblik på at finde nye grupper af stoffer til bekæmpelse af resistente organismer er det usikkert, om og hvornår sådanne stoffer vil være til rådighed. Derfor skal antimikrobielle agenser bruges forsigtigt for at begrænse yderligere forekomst og spredning af resistente kim. Produktudvikling og produktinformation skal spille en betydningsfuld rolle i strategien, og hvis foranstaltningerne til bekæmpelse af antimikrobiel resistens skal lykkes, er der behov for støtte og bidrag fra lægemiddelindustrien samt foranstaltninger på regeringsplan.

På fællesskabsplan har man anerkendt problemet vedrørende antimikrobiel resistens og gjort en indsats for at løse det i de seneste mange år. I dette dokument giver man en **samlet oversigt** over forholdene og beskriver en fællesskabsstrategi for bekæmpelsen af antimikrobiel resistens, herunder forbedrede foranstaltninger til løsning af problemet, som man på internationalt plan, fællesskabsplan og nationalt plan betragter som voksende og som en alvorlig trussel mod sundheden. Af stor betydning er i den sammenhæng Rådets forskellige henstillinger, henstillingerne fra København vedrørende antimikrobiel resistens[1] samt det arbejde, som forskellige internationale organisationer, særligt WHO og OIE (Det Internationale Kontor for Epizootier), udfører.

Kampen mod forekomsten og spredningen af antimikrobiel resistens er således et **prioriteret område inden for folkesundhedsområdet.**

Artikel 152 i traktaten om oprettelse af Det Europæiske Fællesskab udgør retsgrundlaget for foranstaltninger på folkesundhedsområdet. Den bestemmer, at der skal sikres et **højt sundhedsbeskyttelsesniveau** ved fastlæggelsen og gennemførelsen af alle Fællesskabets

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[1] Rapport fra EU-konferencen for særligt indbudte om den mikrobielle trussel, som blev arrangeret af den danske regering i København, Danmark, den 9. - 10. september 1998.

politikker og aktiviteter. Alle Fællesskabets institutioner og medlemsstater er derfor forpligtet af denne bestemmelse.

Spørgsmålet vedrørende antimikrobiel resistens er derfor et grundlæggende element i Fællesskabets sundhedsstrategi, og det indgår i foranstaltningerne vedrørende alle de relevante områder: folkesundheds-, veterinær- og plantesundhedsområdet. Overvågning af antimikrobiel resistens er et af de prioriterede områder i Fællesskabets netværk til epidemiologisk overvågning af og kontrol med overførbare sygdomme. Der er blevet taget mange initiativer og truffet mange foranstaltninger inden for veterinær- og plantesundshedsområdet. Hvad angår lægemidler er denne meddelelse vedlagt Kommissionens forslag til Rådets henstilling om forsigtig anvendelse af antimikrobielle agenser. Det udgør endnu en del af Fællesskabets tværfaglige og mangesidede tilgangsvinkel til bekæmpelse af antimikrobiel resistens.

**En videnskabeligt baseret tilgangsvinkel**

Fællesskabets strategi for antimikrobiel resistens er tværfaglig og baseret på videnskabelig rådgivning.

Den 28. maj 1999 afgav Den Videnskabelige Styringskomité under Europa-Kommissionen en udtalelse om antimikrobiel resistens[2]. Den Videnskabelige Styringskomité udtalte, at der var behov for en hurtig reaktion for på en veltilrettelagt måde at reducere den generelle brug af antimikrobielle agenser på alle områder: lægemidler, veterinærlægemidler, animalsk produktion og plantebeskyttelse. De strategier, som sandsynligvis vil være mest effektive med hensyn til kontrol og begrænsning af antimikrobiel resistens, er dem, som kan indføres hurtigt og uden større omkostninger i alle medlemsstaterne, og som kan overvåges og gennemføres i hele EU. Den Videnskabelige Styringskomité påpegede, at der muligvis er et behov for at indføre effektive love og forordninger, for at målene i forslagene kan nås. De vigtigste indsatsområder, som er blevet udpeget, er forsigtig anvendelse af antimikrobielle agenser, forebyggelse, udvikling af nye metoder til forebyggelse og behandling samt overvågning af effekten af indgrebene.

**En omfattende handlingsplan for bekæmpelse af antimikrobiel resistens**

Kommissionen har på dette grundlag peget på **fire centrale indsatsområder,** som udgør de vigtigste elementer i fællesskabsstrategien for begrænsning af antimikrobiel resistens:

(1) **Overvågning:** Overvågning af udviklingen og effekten af de forskellige indgreb gennem oprettelse/styrkelse af effektive overvågningssystemer vedrørende antimikrobiel resistens hos mennesker og dyr samt forbruget af antimikrobielle agenser.

(2) **Forebyggelse** af overførbare sygdomme og infektionskontrol med henblik på at mindske behovet for antimikrobielle agenser. Det omfatter forsigtig anvendelse af antimikrobielle agenser, hvilket medfører et behov for forbedret produktinformation vedrørende antibakterielle lægemidler og fremme af foranstaltninger vedrørende uddannelse og adfærd, som er rettet mod fagfolk og offentligheden.

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2 http://europa.eu.int/comm/food/fs/sc/ssc/out50_en.html

(3) **Forskning og produktudvikling:** Nye metoder til forebyggelse og behandling af infektioner samt fortsat støtte til forskning vedrørende nye lægemidler og alternative behandlingsmuligheder.

(4) **Internationalt samarbejde:** Antimikrobiel resistens respekterer ikke landegrænserne. En effektiv strategi kræver tæt samarbejde og høringer med deltagelse af Kommissionen, medlemsstaterne og andre involverede parter, navnlig på internationalt plan.

## 1. OVERVÅGNING, KONTROL OG DATAINDSAMLING

### 1.1. Overvågningsnet vedrørende antimikrobiel resistens

#### *1.1.1. Lægemidler*

Der blev i januar 1999 oprettet et net til epidemiologisk overvågning af og kontrol med overførbare sygdomme i Fællesskabet[3]. Antimikrobiel resistens er et af de prioriterede områder. De to vigtigste søjler i nettet til epidemiologisk overvågning af og kontrol med overførbare sygdomme i Fællesskabet er et system for tidlig varsling af og reaktion på trusler mod folkesundheden og et epidemiologisk overvågningssystem for overførbare sygdomme.

Overvågning af overførbare sygdomme, navnlig kontrol af udbrud og rettidig udveksling af relevante oplysninger om tendenser, er af afgørende betydning for interventionsstrategierne for forebyggelse og infektionskontrol. En hurtig og koordineret reaktion fra de offentlige sundhedsmyndigheders side i medlemsstaterne er af afgørende betydning for begrænsningen af den sygelighed og dødelighed, som kunne blive resultatet af infektioner, som spredes hurtigt og ikke respekterer landegrænser. Det kan have stor betydning for begrænsningen af antibiotikabehandling.

En fortsat udvikling af fællesskabsnetværket i løbet af de næste fem år er et vigtigt skridt i retning af en koordineret indsats blandt medlemsstaterne, medlemmerne af EØS/EFTA og kandidatlandene vedrørende forebyggelse af infektioner og begrænsning af resistente organismer.

De specifikke net inden for rammerne af Fællesskabets net omfatter:

- **EARSS - det europæiske overvågningssystem for antimikrobiel resistens[4]**

Sammenligningerne af resistens i de forskellige medlemsstater varierer på grund af forskelle med hensyn til de testede antimikrobielle agenser, de prøver, som er udvalgt til tests, de anvendte systemer til testning af modtagelighed og de vedtagne grænseværdier. For at få mere sammenlignelige og pålidelige data, har Kommissionen støttet det europæiske overvågningssystem for antimikrobiel resistens (EARSS), et internationalt net af nationale overvågningssystemer, som siden 1998 har haft til formål at indsamle sammenlignelige og pålidelige data om antimikrobiel resistens af hensyn til folkesundheden. Nettet vokser. På nuværende tidspunkt har 23 lande indvilliget i at deltage i EARSS: de 15 EU-medlemsstater, Island, Norge, Ungarn, Tjekkiet, Bulgarien, Slovenien, Malta og Israel. Derudover har Estland, Polen, Slovakiet, Rumænien og Rusland givet udtryk for, at de er interesserede i at deltage. Af de deltagende lande har 18 på nuværende tidspunkt indsendt data. Den anslåede gennemsnitlige dækning af befolkningen i de deltagende lande er på 53 % og varierer fra 14 % til 90 %.

Hvad angår fremtidige perspektiver, kunne indsamlingen af data, som udarbejdes rutinemæssigt, fremskynde den proces, som har til formål at tilvejebringe overvågning af flere patogener. Man har gjort fremskridt med hensyn til at tilvejebringe softwareredskaber til udarbejdelse og analyse af data vedrørende resistens. Næste trin er at gøre disse data

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[3] Beslutning nr. 2119/98/EF, EFT L 268 af 3. oktober 1998.

[4] http://www.earss.rivm.nl

almindeligt tilgængelige gennem EUPHIN-HSSCD (Health Surveillance System for Communicable Diseases within the European Public Health Information Network).

- **Enter-Net - Internationalt overvågningsnet for enteriske infektioner - Salmonella og VTEC 0157**[5]

Enter-net blev oprettet i 1994 til overvågning af infektioner med salmonella og verotoksinproducerende escherichia coli (VTEC). Siden 2000 har det været en betydningsfuld del af nettet til epidemiologisk overvågning af og kontrol med overførbare sygdomme i Fællesskabet. Et af de vigtigste formål er hurtig påvisning af sygdomsudbrud. Enter-net har bidraget direkte til påvisningen af adskillige internationale sygdomsudbrud og har gjort det muligt at gennemføre de efterfølgende undersøgelser hurtigt på grund den effektive kommunikation og det effektive samarbejde inden for nettet. Inden for nettet beskæftiger man sig også med overvågning af antibiotikaresistens hos enteriske patogener.

- **Euro-TB**[6]

Det overordnede formål med programmet Euro-TB til overvågning af tuberkulose i Europa er at tilvejebringe epidemiologiske oplysninger om tuberkulose (TB), som skal anvendes til at forbedre TB-kontrollen. Resistens over for lægemidler er en af de vigtigste faktorer i tuberkuloseovervågningen. Udbredelsen heraf, navnlig af resistens over for mange lægemidler (multiresistens), er af stor betydning for folkesundheden, da multiresistent TB udgør en væsentlig epidemiologisk risiko, navnlig for personer med svækket immunforsvar som f.eks. HIV-smittede og personer, som befinder sig i institutioner som f.eks. hospitaler og plejecentre. Overvågning af resistens over for lægemidler er et vigtigt redskab, som gør det muligt at tilvejebringe målrettede kontrolforanstaltninger med henblik på at reducere forekomsten. Under programmet Euro-TB koordineres udarbejdelsen af henstillinger vedrørende standardisering af overvågningen af resistens over for lægemidler relateret til tuberkulose i Europa.

- **Nosokomielle infektioner**

Nosokomielle infektioner er infektioner hos en patient på et hospital, som ikke var til stede hos den pågældende patient, og som heller ikke var i sin inkubationstid, da patienten blev indlagt, men som denne efterfølgende har pådraget sig. De kan også forekomme hos hospitalspersonale.

I 2000 påbegyndte man et pilotprojekt for at udvikle et europæisk net vedrørende nosokomielle infektioner. Hovedformålene omfatter oprettelsen af databaser om infektioner på kirurgiske afdelinger og intensivafdelinger, tilvejebringelse af enighed om undersøgelser vedrørende forekomsten, validering af metoderne til udarbejdelse af dokumenterede standarder og anbefalinger samt tilvejebringelse af betingelserne for udvidede fælles undersøgelser, uddannelse og stipendier.

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5 http://www2.phls.co.uk

6 http://www.ceses.org/eurotb.htm

### *1.1.2. Veterinærmedicin*

- **Overvågning og kontrol af zoonoser**[7]

Fællesskabslovgivningen om foranstaltninger mod zoonoser[8], som for tiden revideres, har til formål at tilvejebringe et pålideligt rapporteringssystem vedrørende forekomsten af zoonoser hos dyr og mennesker. På nuværende tidspunkt dækker de specifikke kontrolforanstaltninger i direktivet kun forekomsten af to invasive serotyper af *Salmonella* i avlsflokke af fjerkræ, som ofte er kilde til salmonellose hos mennesker, der har spist æg. Der er blevet oprettet to EU-referencelaboratorier, som skal koordinere og harmonisere de nationale laboratoriers arbejde og indsamle oplysninger om zoonoser, herunder oplysninger om antimikrobiel resistens hos zoonotiske bakterier.

Medlemsstaterne har hvert år siden 1995 indsendt rapporter om forekomsten af visse zoonotiske organismer. Indsamlingen af oplysninger om resistens i forbindelse med rapporterne er dog endnu ikke blevet harmoniseret, og metoderne til testning af resistens varierer fra medlemsstat til medlemsstat.

Ud over disse horisontale bestemmelser indeholder forskellige direktiver om dyresundhedsmæssige betingelser bestemmelser om kravene til kontrollen af visse zoonoser (f.eks. tuberkulose og brucellose) på bedrifterne. Specifikke foranstaltninger til bekæmpelse af zoonotiske agenser ved fremstilling og distribution af animalske fødevarer er fastsat i de tilsvarende hygiejnedirektiver.

Kommissionen har tydeligt påpeget, at fødevaresikkerhed er et af de vigtigste prioriterede områder. I hvidbogen om fødevaresikkerhed[9] beskriver man planerne for en proaktiv ny fødevarepolitik, som følger princippet om "jord til bord" ved navnlig at modernisere lovgivningen, således at der udarbejdes et sæt sammenhængende og gennemsigtige regler med henblik på at få sikrere fødevarer fra sundere dyr. Denne politik skal tage hensyn til udbredelsen af zoonotiske agenser i medlemsstaterne og garantere bedre forbrugersikkerhed ved at indføre programmer for reduktion af patogener, som skal gennemføres af medlemsstaterne.

Inden for rammerne af revisionen af zoonoselovgivningen overvejer Kommissionen muligheden for at indføre et krav om overvågning af antimikrobiel resistens hos visse zoonotiske mikroorganismer som f.eks. salmonella og campylobacter i visse dyrepopulationer. Et forslag til ny lovgivning, som skal forbedre overvågningen af og rapporteringen vedrørende systemer for sygdomme, som kan overføres fra dyr til mennesker, forventes at blive forelagt i 2001.

- **Overvågning af antimikrobiel resistens**

Bortset fra initiativerne vedrørende zoonotiske agenser er overvågning af antibiotikaresistens hos bakterier med animalsk oprindelse en samordnet indsats[10] i Fællesskabet. Indsatsen har til formål at harmonisere overvågningen af antibiotikaresistens i Europa og at udvikle forskningsprojekter, som skal føre til, at man får en bedre forståelse af de mekanismer, der

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7 Alle sygdomme og/eller infektioner, der naturligt direkte eller indirekte kan overføres fra dyr til mennesker.

8 Rådets direktiv 92/117/EØF, EFT L 62 af 15. marts 1993

9 http://europa.eu.int/comm/dgs/health_consumer/library/pub/pub06_en.pdf

10 FAIR5-CT97-3654.

ligger til grund for forekomsten og spredningen af resistens hos en art samt spredningen fra dyr til mennesker og miljøet.

Kommissionen indførte i januar 1997 kravet om at overvåge resistensen hos bakterier med animalsk oprindelse fra antibiotika i tilsætningsstoffer til foderstoffer og lignende stoffer i Kommissionens direktiv[11] om suspension af anvendelsen af avoparcin som et tilsætningsstof til foderstoffer. Kravet blev bekræftet i Rådets forordning[12] af december 1998 om suspension af anvendelsen af fire andre antibiotika, som anvendes som vækstfremmere i foderstoffer, som et krav for at undersøge spørgsmålet igen.

Kommissionen har også støttet et industristyret overvågningsprogram vedrørende resistens over for antibiotika, der anvendes som tilsætningsstoffer til foderstoffer, hos bakterier fra svin og slagtekyllinger fra slagterier i seks europæiske lande. Der vil være en rapport til rådighed om kort tid.

Man bør dog sikre, at der etableres overvågningssystemer, som sikrer, at der indsamles oplysninger om resistens hos alle relevante bakterier hos dyr og i foderstoffer på fællesskabsplan.

## 1.2. Overvågning af antibiotikaforbruget

### *1.2.1. Mennesker*

I forbindelse med udviklingen af interventionsstrategier er der behov for pålidelige oplysninger om forbruget af antimikrobielle agenser. Sådanne oplysninger findes allerede i mange af medlemsstaterne, men de er spredte, uensartede og i mange tilfælde ikke umiddelbart tilgængelige. Man skal have adgang til oplysningerne, således at de kan blive indsamlet og analyseret med henblik på at gøre det muligt at udvikle et EU-overvågningssystem vedrørende brugen af antimikrobielle agenser og procedurer for interventionsforanstaltninger. Kommissionens forslag til Rådets henstilling om forsigtig anvendelse af antimikrobielle agenser i lægemidler, som er vedlagt, behandler dette problem.

### *1.2.2. Dyr*

- **Veterinærlægemidler**

Kun nogle få medlemsstater overvåger på nuværende tidspunkt forbruget af antimikrobielle agenser, som anvendes som veterinærlægemidler. Denne type oplysninger om forbruget er ikke desto mindre af afgørende betydning for vurderingen af den risiko, som hidrører fra overførslen af resistente mikroorganismer af animalsk oprindelse til mennesker. I forbindelse med dette aspekt bør man overveje yderlige foranstaltninger på fællesskabsplan.

- **Tilsætningsstoffer i foderstoffer**

Efter henstillingerne fra København har man etableret et system til indsamling af oplysninger om udbuddet og forbruget af antimikrobielle agenser som tilsætningsstoffer i foderstoffer, både som veterinærlægemidler og vækstfremmere. På grundlag retningslinjerne for indsamling af relevante oplysninger, som man har vedtaget i Den Stående Foderstofkomité,

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11 Direktiv 97/6/EF, EFT L 35 af 5. februar 1997.

12 Forordning 2821/98, EFT L 351 af 29. december 1998.

begyndte man overvågningen i januar 2000. De første resultater skulle være til rådighed i midten af 2001.

*1.2.3. Plantebeskyttelse*

Brugen af antibiotika til plantebeskyttelse overvåges i alle de medlemsstater, hvor en sådan brug finder sted. Der findes et totalt forbud mod antibiotika i Sverige, Finland, Italien, Portugal, Irland, Luxembourg, Danmark, Frankrig, Det Forenede Kongerige og Tyskland. Den Stående Komite for Plantesundhed fastlagde allerede i 1999 en procedure for indsamling af oplysninger i de medlemsstater, der stadig tillader brugen i nødsituationer, og der er adgang til disse oplysninger.

### 1.3. Sikkerhedsevaluering af antimikrobielle agenser som anvendes til plantebeskyttelse

Fællesskabslovgivningen om plantebeskyttelsesprodukter[13] udgør også retsgrundlaget for evalueringen af antibiotika, som anvendes til plantebeskyttelse. Alle de krav til oplysninger og kriterier for beslutningstagningen, som findes i direktivet, finder i princippet også anvendelse i forbindelse med de antibiotika, som anvendes. På baggrund af forbuddet mod en sådan anvendelse i de fleste af medlemsstaterne og de ringe mængder, som anvendes, samt de begrænsninger, som findes i andre medlemsstater, har Kommissionen dog fastlagt andre prioriterede områder i forbindelse med det igangværende revisionsprogram under direktivet. Antibiotika, som på nuværende tidspunkt anvendes i Fællesskabet, bliver revideret i forbindelse med tredje fase af revisionsprogrammet, som påbegyndes i 2002.

Fungicider er tilladte i alle medlemsstaterne, og de aktive stoffer revideres i forbindelse med de igangværende programmer under direktiv 91/414/EØF.

## 2. MOD ET FORBEDRET SYSTEM FOR FOREBYGGELSE OG KONTROL

### 2.1. Markedsføringstilladelse og oplysninger til brugerne om antimikrobielle agenser

*2.1.1. Lægemidler*

Det Europæiske Agentur for Lægemiddelvurdering er involveret i en række aktiviteter, som drejer sig om markedsføringstilladelse samt kvaliteten og indholdet af resuméet af produktets egenskaber, som især udgør grundlaget for alle de salgsfremmende foranstaltninger vedrørende et antimikrobielt agens.

Det Europæiske Agentur for Lægemiddelvurdering har offentliggjort et debatoplæg vedrørende antimikrobiel resistens[14], hvori man beskriver agenturets aktiviteter og understreger behovet for at finde metoder til fremme af nye effektive antibiotika, således at man ikke på et for tidligt tidspunkt udtømmer disses kliniske potentiale.

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[13] Direktiv 91/414/EØF, EFT L 230 af 19. august 1991.

[14] Dokument fra Det Europæiske Agentur for Lægemiddelvurdering nr. 9880/99: http://www.eudra.org/humandocs/humans/general.htm

Kriterierne for markedsføringstilladelse til nye antibakterielle lægemidler er beskrevet i tre dokumenter med retningslinjer fra EU, som blev operationelle i 1997 og 2000 (14-16)[15]. Navnlig oplysninger om opnået resistens vedrørende relevante kombinationer af bakterier/antibiotika skal ajourføres jævnligt af den eller de personer eller virksomheder, som har markedsføringstilladelsen. Et bedre grundlag for at give anbefalinger om dosering af antibiotika er også blevet beskrevet i en af retningslinjerne. Man kan antage, at bedre anbefalinger om doseringen vil bidrage til en optimal behandling af infektioner og en nedbringelse af den unødvendige og uhensigtsmæssige brug af antibiotika.

De for reguleringen ansvarlige hos de forskellige europæiske myndigheder har udtrykt bekymring over, at der findes forskelle med hensyn til anvisninger, doser, indgivelsens varighed (behandlingens varighed) og forskellige farmakodynamiske oplysninger vedrørende det samme og lignende produkter, som man allerede har givet tilladelse til i EU. De nationale myndigheder drøfter for nærværende spørgsmålet vedrørende modstridende produktoplysninger i samarbejde med Det Europæiske Agentur for Lægemiddelvurdering.

*2.1.2. Veterinærmedicin*

Det skal i forbindelse med tilladelsen til veterinærlægemidler sikres, at anbefalingerne vedrørende doseringen og behandlingens varighed er optimale, således at udviklingen af resistens holdes på et minimum. Derudover kan det være nødvendigt at overvåge mønstrene for følsomhed hos populationer af målbakterierne, efter at tilladelsen er givet.

Udvalget for Veterinærlægemidler under Det Europæiske Agentur for Lægemiddelvurdering understregede i sin rapport vedrørende antimikrobiel resistens og kvalitativ risikovurdering, at langt størstedelen af den antibiotika, som anvendes i veterinærmedicin, er relateret til eller identisk med lægemidler til mennesker og kan være enten krydsresistente eller samtidigt resistente. Det pegede også på, at der er mangel på oplysninger og harmonisering, hvilket er til hinder for en sammenhængende og videnskabelig tilgangsvinkel på europæisk plan. Derudover har man udarbejdet en strategisk risikostyringsplan, hvori man beskriver forslag vedrørende begrænsning af antimikrobiel resistens, og følgende hovedområder under Udvalget for Veterinærlægemidlers aktiviteter planlægges for øjeblikket:

a) Kritisk evaluering af data vedrørende mindste hæmmende koncentration samt af den nuværende relevans af at anvende mindste hæmmende koncentration og kinetiske data i forbindelse med fastsættelsen af doseringerne.

b) Udvikling af retningslinjer for at leve op til kravene om et afsnit om resistens i et regelværk vedrørende antimikrobielle agenser med særlig vægt på en beskrivelse af den testning, som har til formål at fastslå sandsynligheden for udvikling af resistens hos nye antimikrobielle agenser, dvs. retningslinjer for den følsomhedsanalyse, som gennemføres før godkendelsen.

c) Konsolidering og standardisering af de termer og formater, som anvendes i resumeet af produktegenskaberne med henblik på tydeligt og ensartet at definere doseringen/behandlingen, målorganismerne og sygdommene i overensstemmelse med principperne vedrørende forsigtig brug i hele EU.

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[15] Følgende dokumenter fra Det Europæiske Agentur for Lægemiddelvurdering: CPMP/EWP/558/95, CPMP/EWP/520/96, CPMP/EWP/2655/99.

d) Udvikling af endelige retningslinjer for antimikrobiel profylakse, kombinationsbehandlinger og lægemidler som gives i foder og vand, da resistensen er afhængig af omfanget af den aktive brug og administrationsmåden.

## 2.2. Forsigtig anvendelse af antimikrobielle agenser

### *2.2.1. Lægemidler: Kommissionens forslag til Rådets henstilling*

Kommissionen har udarbejdet et forslag til Rådets henstilling om forsigtig anvendelse af antimikrobielle agenser i lægemidler til mennesker, som er vedlagt denne meddelelse.

De vigtigste elementer i forslaget er som følger:

- **Indsamling og analyse af oplysninger** om patogener, som er resistente over for antimikrobielle agenser, og om forbruget af antimikrobielle agenser med henblik på at bestemme mulige forbindelser til brug i forbindelse med interventionsforanstaltningerne.

- Håndhævelse af princippet om at antibakterielle stoffer **kun kan fås på recept,** og vurdering af om denne regel som en forebyggende foranstaltning skal finde anvendelse over for alle antimikrobielle agenser.

- Udvikling af retningslinjer og principper for **forsigtig brug** af antimikrobielle agenser, herunder evalueringssystemer.

- Forbedring af **forebyggelsen** af infektioner med henblik på at formindske behovet for antimikrobielle agenser ved at styrke immuniseringsprogrammerne og udvikle standarder for infektionskontrol på hospitalerne og i samfundet som sådan.

- Forøgelse af kendskabet til problemet vedrørende antimikrobiel resistens ved hjælp af **oplysningsaktiviteter rettet mod offentligheden.**

- Forøgelse af kendskabet til problemet ved hjælp af uddannelsesprogrammer rettet mod ansatte i sundhedssektoren.

- Fremme af **forskning** i udviklingen af antimikrobiel resistens samt udviklingen af hurtige diagnoser med henblik på at gøre det muligt at gennemføre en effektiv og tidlig behandling af overførbare sygdomme.

- I den forbindelse udpegelse af en national organisation, som arbejder på tværs af fag og sektorer, med henblik på at sikre gensidig udveksling af oplysninger og **koordinering** af arbejdet.

### *2.2.2. Veterinærmedicin*

Overvågningen af restkoncentrationer i fødevarer er et vigtigt element i forbindelse med sikringen af forsigtig anvendelse af antimikrobielle agenser i veterinærmedicin. I fællesskabslovgivningen[16] kræves det, at man overvåger visse stoffer (herunder antimikrobielle agenser) eller restkoncentrationer i levende dyr og animalske produkter. Omfanget af prøvedudtagningen er fastsat i Rådets direktiv 96/23/EF, og de størst tilladte restkoncentrationer fastsættes i henhold til forordning (EØF) 2377/90 på grundlag af

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[16] Rådets direktiv 96/23/EF, EFT L 125 af 23. april 1996.

videnskabelig rådgivning. Medlemsstaterne og tredjelande (i forbindelse med de produkter, som de eksporterer til EU) indsender til Kommissionen de årlige resultater af overvågningen i henhold til deres restkoncentrationsplaner, som er blevet godkendt af Kommissionen. Overholdelsen af fællesskabsreglerne kontrolleres desuden jævnligt på stedet af Kommissionens Levnedsmiddel- og Veterinærkontor.

På nuværende tidspunkt udgør antallet af prøver med positive resultater mindre end 1 % af det samlede antal. Det drejer sig dog om fund af antibiotika for ca. 70 % af de positive prøvers vedkommende. Selv om den gældende lovgivning ved hjælp af direktiv 81/851/EØF og 81/852/EØF fastsætter harmoniserede krav til markedsføringstilladelser i EU, og forordning (EØF) 2377/90 sikrer en harmoniseret procedure for udstedning af tilladelser til analysemetoder, betyder det betragtelige antal stoffer, som man har givet markedsføringstilladelse til i de senere år, at der er behov for, at de nationale kompetente myndigheder sammen med Det Europæiske Agentur for Lægemiddelvurdering drøfter spørgsmålet vedrørende modstridende produktoplysninger yderligere.

Der er blevet truffet adskillige offentlige og private foranstaltninger i medlemsstaterne og på det internationale og europæiske plan for at udarbejde retningslinjer for forsigtig anvendelse af antimikrobielle agenser som veterinærmedicin. For eksempel har den europæiske sammenslutning for dyrlæger udarbejdet en vejledning i forsigtig anvendelse af antibiotika i veterinærmedicin, og derudover har visse medlemsstater deres egne nationale retningslinjer. Også Det Internationale Kontor for Epizootier (OIE) og Codex Alimentarius behandler på nuværende tidspunkt spørgsmål vedrørende forsigtig anvendelse af antimikrobielle agenser i forbindelse med dyr, og OIE har netop offentliggjort en række principper for forsigtig anvendelse. Med henblik på at harmonisere aktiviteterne på fællesskabsplan bør man drøfte, om der på veterinærområdet er behov for foranstaltninger, som er sammenlignelige med dem, som er foreslået i henstillingen om forsigtig anvendelse i lægemidler til mennesker. Navnlig bør man lægge vægt på at forebygge overførbare sygdomme hos dyr, da man således mindsker forbruget af antimikrobielle agenser effektivt. Derudover er det af afgørende betydning at opfordre medlemsstaterne til at styrke deres kontrol af illegal distribution af antimikrobielle agenser i landbruget, da man således mindsker muligheden for uhensigtsmæssig anvendelse af stofferne.

## 2.3. Tilsætningsstoffer

### *2.3.1. Tilsætningsstoffer i fødevarer*

Anvendelsen af tilsætningsstoffer i fødevarer er harmoniseret i EU. Fællesskabslovgivningen vedrørende tilsætningsstoffer i fødevarer[17] fastsætter principperne for godkendelse af tilsætningsstoffer og anvendelse heraf i fødevarer. Det er tilladt at anvende to antimikrobielle agenser, nisin (E 234) og natamycin (E 235), til konservering af visse fødevarer. Kommissionen reviderer sikkerheden og behovet for at anvende stofferne.

### *2.3.2. Udfasning og erstatning af antimikrobielle agenser, som anvendes som vækstfremmere i foder*

Kommissionen er i stigende grad opmærksom på kun at anvende antibiotika i tilfælde af alvorlige sundhedsmæssige problemer hos mennesker eller dyr. Antallet af forskellige antibiotika, som det er tilladt at anvende som vækstfremmere i dyrs ernæring, har da også været konstant faldende. Efter forbuddet mod avoparcin i januar 1997, ardacin i januar 1998

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[17] Rådets direktiv 89/107/EØF, EFT L 40 af 11. februar 1989.

og yderligere fire antibiotika i december 1998 (zinkbacitracin, virginiamycin, tylosinfosfat og spiramycin) findes der kun fire stoffer, som stadig er tilladte som vækstfremmende agenser. Stofferne hører ikke ind under de klasser, som anvendes i forbindelse med lægemidler og/eller veterinærmedicin. Efter en gennemgang af yderligere dokumentation har Den Videnskabelige Styringskomité for nylig konkluderet, at den dokumentation, som lå til grund for det oprindelige forbud, stadig er gyldig.

Som beskrevet i hvidbogen om fødevaresikkerhed tilstræber Kommissionen dog et forbud mod eller en udfasning af antibiotika, som anvendes som vækstfremmere i EU, som en del sin brede strategi for kontrol med og begrænsning af antibiotikaresistens.

I mellemtiden er det dog nødvendigt at gennemføre undersøgelser af de mest kritiske sektorer (navnlig produktion af smågrise og slagtekyllinger) for at minimere risikoen for økonomiske tab eller en forøgelse af anvendelsen af antibiotika til behandling, efter at en dyrlæge har udstedt en recept. I forbindelse med undersøgelserne skal det vurderes, hvor stor en forskel der er mellem den nuværende situation og de opdrætsstandarder, som bliver påkrævede efter et forbud mod antimikrobielle vækstfremmere træder i kraft.

Kommissionen deler det synspunkt, at en udfasning også ville være lettere at gennemføre, hvis andre typer af vækstfremmende tilsætningsstoffer blev tilgængelige. I den forbindelse har man givet tilladelse til 19 forskellige mikroorganismer indtil videre, og man er meget tæt på at give tilladelse til en række andre mikroorganismer. Man er ved at undersøge en ansøgning om tilladelse til at anvende organisk syre som vækstfremmer, og medlemsstaterne har modtaget adskillige andre ansøgninger om tilladelse til at anvende andre typer produkter, som har en positiv effekt på den animalske produktion.

Et forslag om at udfase de øvrige fire antimikrobielle tilsætningsstoffer i foderstoffer senest i januar 2006 er under udarbejdelse og forventes at blive vedtaget af Kommissionen i den nærmeste fremtid.

## 2.4. Antimikrobiel resistens som markør for genetisk modificerede organismer

Den Videnskabelige Styringskomité har anbefalet at fjerne markørgener for antibiotikaresistens fra planteceller, før de markedsføres, i videst muligt omfang. Mens dette er muligt i forbindelse med nyere produkter, er det svært eller umuligt i forbindelse med ældre produkter. Den kliniske betydning af det pågældende antibiotikum og promotorgen, en regulerende DNA-sekvens, som har til funktion at aktivere ekspression af gener, skal i sidstnævnte tilfælde tages i betragtning, før der gives nogen tilladelse.

Fællesskabslovgivningen om udsætning i miljøet af genetisk modificerede organismer er blevet revideret for nylig, og det nye direktiv 2001/18/EF trådte i kraft den 17. april 2001[18]. Medlemsstaterne skal gennemføre direktivet i den nationale lovgivning senest den 17. oktober 2002. Direktiv 2001/18/EF bestemmer, at medlemsstaterne og Kommissionen skal sikre, at GMO'er, der indeholder gener, som udtrykker resistens over for antibiotika anvendt i human- eller veterinærmedicinsk behandling, tages specielt i betragtning ved miljørisikovurderingen med henblik på identifikation og udfasning af antibiotikaresistensmarkører i GMO'er, der kan have uønskede virkninger på menneskers sundhed og miljøet.

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[18] EFT L 106 af 17. april 2001.

## 3. FORBEREDELSE AF FREMTIDEN

Forskning vedrørende antimikrobiel resistens har i lang tid været en del af Fællesskabets forskning. Inden for rammerne af det fjerde rammeprogram for forskning og teknologisk udvikling (1994-1998)[19] og det nuværende femte rammeprogram (1998-2002)[20] bidrager adskillige projekter direkte eller indirekte til de forskellige søjler i en mellemlang- til langsigtet tilgangsvinkel til bekæmpelse af antibiotikaresistens. De fleste af de relevante forskningsemner dækkes af nøgleaktion 2 "bekæmpelse af smitsomme sygdomme" i programmet for livskvalitet, hvor man i igangværende forskningsprojekter behandler følgende emner:

- **Vacciner** mod tuberkulose, malaria, HIV og andre alvorlige sygdomme med henblik på i sidste ende at reducere morbiditeten og dermed behovet for antimikrobiel behandling.

- Udvikling af **nye typer antimikrobielle agenser** mod multiresistente stammer af farlige patogener (f.eks. *Mycobacterium tuberculosis*) og andre nye behandlingsstrategier som f.eks. konjugationsinhibitorer eller effluxinhibitorer.

- Udvikling af **hurtige og pålidelige diagnose- og sandsynlighedsforsøg** som en væsentlig forudsætning for forsigtighed i forbindelse med, at der udskrives recepter på antibiotika.

- Bestemmelse af **nye strategier til begrænsning af spredningen af infektioner** i daginstitutioner.

- Øget kendskab til de molekylære mekanismer bag udviklingen, spredningen og reversibiliteten af antibiotikaresistens.

- Evaluering og harmonisering af strategierne til forebyggelse og begrænsning af antibiotikaresistente patogener på de europæiske hospitaler.

Andre nøgleaktioner under programmet for livskvalitet behandler emner, som supplerer de ovenfor beskrevne prioriterede områder. Nøgleaktion 1 vedrørende fødevarer, ernæring og sundhed drejer sig om de mekanismer, som overfører antibiotikaresistens mellem animalske, mikrobielle og humane værter via indtagelse af mad; udvikling og validering af hurtige og/eller omkostningseffektive tests for påvisning af antibiotika; samt kombinationer af probiotika som alternativer til de nuværende antibiotika. Nøgleaktion 3 vedrørende "cellefabrikken" drejer sig om udformning og udvikling af nye **antimikrobielle agenser** samt patientnære diagnostiske prøver, og nøgleaktion 4 vedrørende miljø og sundhed drejer sig om miljømæssige faktorer, som påvirker overførslen. Nøgleaktion 5 vedrørende bæredygtigt landbrug, fiskeri og skovbrug og integreret udvikling af landbrugsdistrikterne, herunder bjergområder, har til formål at tilvejebringe nye strategier for reducering af anvendelsen af antibiotika i forbindelse med husdyropdræt.

Det Fælles Forskningscenter under Kommissionen deltager i udviklingen af analysemetoder og referencemateriale, som skal anvendes til påvisning af restkoncentrationer af antibiotika i forskellige fødevarer og foderstoffer.

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19 EFT L 126 af 18. maj 1994.

20 EFT L 26 af 1. februar 1999.

Kommissionen har forelagt sit forslag til det næste rammeprogram (2002-2006)[21], hvori man fremhæver bekæmpelsen af resistens over for lægemidler som et prioriteret område.

## 4. INTERNATIONALT SAMARBEJDE

En enorm forøgelse af den globale handel og rejseaktivitet har forøget den hastighed, hvormed sygdomme og antimikrobiel resistens spredes mellem lande og kontinenter. Antimikrobiel resistens respekterer ikke grænserne og er af betydning for hele verden; problemet kan ikke med held tackles af et enkelt land eller for den sags skyld en gruppe lande. Samordnede internationale foranstaltninger er derfor et vigtigt element i løsningen af problemet.

Man har allerede et intensivt samarbejde med en del lande uden for EU. I forbindelse med den fremtidige udvidelse af EU har man lagt særlig vægt på samarbejde med ansøgerlandene, som allerede deltager i en række sundhedsprogrammer og de fleste af de europæiske overvågningsnet.

Det er også nødvendigt, at udviklingslandene deltager, og man giver dem da også støtte inden for alle områder af bekæmpelsen af antimikrobiel resistens: overvågningsnet, dataindsamling, forskning og procedurerne for udstedelse af tilladelser til nye typer medicin og vacciner, sygdomsforebyggelse samt uddannelse af ordinerende læger. Man bør også bemærke Fællesskabets udviklingspolitik[22]. Man giver også støtte til bekæmpelsen af ulovlig kopimedicin, som udover at forårsage økonomiske tab i medicinalindustrien også har stor betydning for spredningen af antimikrobiel resistens (uhensigtsmæssig dosering og varighed af behandlingen, reducering af effektiviteten).

Det internationale samarbejde kræver involvering af de nationale regeringer og regeringskontorer, ikke-statslige organisationer, erhvervssammenslutninger og internationale institutter. Det skal skabe en synergieffekt, og man skal undgå modstridende oplysninger. Data og oplysninger om erfaringer skal udveksles mellem alle parterne med henblik på, at man kan få størst muligt udbytte af alle strategierne. Man skal også opnå store fremskridt med hensyn til harmoniseringen af dataindsamlingen med henblik på, at man kan blive i stand til at udnytte disse data på internationalt plan.

I den sammenhæng har Kommissionen etableret en række vigtige forbindelser:

- **Verdenssundhedsorganisationen** (WHO) og Europa-Kommissionen har for nylig genbekræftet deres fælles interesse i sundhed og sundhedsrelaterede områder ved at underskrive et aftalememorandum. Som prioriterede områder i forbindelse med det fremtidige samarbejde har man vedtaget at skabe forbindelse mellem net for overførbare sygdomme og net for sundhedsovervågning og at udvikle metodologier og standarder for bekæmpelsen af de med antimikrobiel resistens forbundne trusler. WHO har deltaget i udarbejdelsen af forslaget til Rådets henstilling om forsigtig anvendelse af **antimikrobielle agenser** i lægemidler til mennesker, som er vedlagt denne meddelelse. Kommissionen bidrager til WHO's aktiviteter vedrørende fastlæggelse af en global strategi for begrænsning af antimikrobiel resistens.

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21 EFT ...

22 KOM(2000) 585 endelig og KOM(2001) 96 endelig.

- **Codex Alimentarius** beskæftiger sig også med antimikrobiel resistens, navnlig hvad angår de højest tilladte restkoncentrationer i fødevarer. Der er blevet taget initiativ til, at Fællesskabet skal blive medlem af Codex Alimentarius som sådan sammen med medlemsstaterne, og man vil fremme en samordnet og harmoniseret tilgangsvinkel.

- ***Office International des Epizooties*** (OIE - den internationale organisation for dyresundhed) har tydeligt påpeget, at antimikrobiel resistens er et af organisationens prioriterede områder i de kommende år, og gennemført en verdensomspændende høring om dens anbefalinger vedrørende begrænsning af antibiotikaresistens.

- Der blev i 1995 oprettet en **EU-USA-taskforce vedrørende overførbare sygdomme** som led i EU-USA-handlingsplanen for gennemførelsen af den nye transatlantiske dagsorden. Arbejde vedrørende bekæmpelse af antimikrobiel resistens er et prioriteret område for EU-USA-taskforcen, og man har i den forbindelse oprettet en særlig arbejdsgruppe.

- I juni 2000 vedtog EU's stats- og regeringschefer **handlingsplanen vedrørende den nordlige dimension** og opfordrede Europa-Kommissionen til at spille en fremtrædende rolle i forbindelse med gennemførelsen. I forbindelse med målene vedrørende folkesundhed beskrives overvågning og begrænsning af overførbare sygdomme, herunder foranstaltninger vedrørende antimikrobiel resistens, som prioriterede områder.

- **De baltiske landes task force for kontrol med overførbare sygdomme** udstedte anbefalinger vedrørende antibiotikaresistens på sit sidste møde i slutningen af 2000 i København: receptpligtige lægemidler, indsamling og udveksling af data, forbedring af diagnoserne, overvågningsnet og systemer for tidlig varsling samt uddannelse af personalet.

- På den første Euro-Middelhavskonference for sundhedsministrene i Montpellier den 3. december 1999 vedtog man, at netværket til epidemiologisk overvågning af og kontrol med smitsomme sygdomme i Det Europæiske Fællesskab er et vigtigt element i styrkelsen af samarbejdet vedrørende folkesundhed.

# KONKLUSION

I den følgende liste beskrives de prioriterede aktiviteter inden for de **fire nøgleområder, som man har fastlagt** under fællesskabsstrategien mod antimikrobiel resistens, som supplerer den specifikke henstilling om forsigtig anvendelse af antimikrobielle agenser.

**Overvågning**

Aktivitet 1: Udvikling af koordinerede og sammenhængende overvågningsnet på europæisk plan. Fremme af deltagelsen af lande uden for EU og forbindelserne mellem allerede oprettede overvågningsnet inden for områderne lægemidler og veterinærmedicin.

Aktivitet 2: Etablering og forbedring af indsamlingen af data om forbrug af **antimikrobielle agenser** i alle sektorer.

**Forebyggelse**

Aktivitet 3: Forøgelse af betydningen af oplysninger om antimikrobiel resistens i forbindelse med processen for udstedelse af markedsføringstilladelser vedrørende lægemidler, veterinærmedicin og landbruget.

Aktivitet 4: Støtte på fællesskabsplan til uddannelseskampagner rettet mod de berørte erhverv (klinikere, dyrlæger og landbrugere) og offentligheden med henblik på at undgå overforbrug og misbrug af antimikrobielle agenser.

Aktivitet 5: Fuldstændig gennemførelse af princippet om, at antibakterielle stoffer kun kan anvendes i receptpligtige lægemidler og veterinærmedicin og distribueres under kontrol i landbrugssektoren samt evaluering af om reglen vedrørende receptpligt skal omfatte alle **antimikrobielle agenser** af forsigtighedshensyn.

Aktivitet 6: Styrkelse og fremme af forebyggelsesprogrammer vedrørende infektioner inden for områderne lægemidler og veterinærmedicin, navnlig immuniseringsprogrammer.

Aktivitet 7: Styrkelse af overvågningssystemet for restkoncentrationer i fødevarer, hvad angår analysemetoder, sanktioner og rapporteringssystemer.

Aktivitet 8: Udfasning og erstatning af **antimikrobielle agenser**, som anvendes som vækstfremmere i foder.

Aktivitet 9: Revidering af anvendelsen af de to tilladte antimikrobielle agenser i fødevarer.

Aktivitet 10: Sikring af at GMO'er, der indeholder gener, som er resistente over for antibiotika anvendt i human- eller veterinærmedicinsk behandling, tages specielt i betragtning ved miljørisikovurderingen med henblik på identifikation og udfasning af antibiotikaresistensmarkører i GMO'er, der kan have uønskede virkninger på menneskers sundhed og miljøet.

**Forskning og produktudvikling**

Aktivitet 11: Fremme af udviklingen af nye **antimikrobielle agenser.**

Aktivitet 12: Fremme af udviklingen af alternative behandlinger og vacciner.

Aktivitet 13: Støtte til udviklingen af hurtige og pålidelige diagnose- og sandsynlighedsforsøg.

**Internationalt samarbejde**

Aktivitet 14: En stor indsats for at udvikle samarbejde, koordinering og partnerskaber på internationalt plan, navnlig gennem de eksisterende internationale organisationer.

Aktivitet 15: Særlig fokus på ansøger- og udviklingslandene ved at hjælpe dem med at etablere hensigtsmæssige strukturer.

European Medicines Agency

EMEA/CVMP/56937/2007- Final
22 February 2007

# COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE AND COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

## Presence of the antibiotic resistance marker gene nptII in GM plants for food and feed uses

### Background

In a letter dated 25 January 2007, Mr Robert Madelin from the Directorate General for Health and Consumer Protection of the European Commission informed the EMEA that the Commission was considering the authorisation for the placing on the market of the genetically modified potato line EH92-527-1 which contains a genetic modification that harbours an *nptII* gene as a selectable marker. This gene codes for neomycin phosphotranserase, an enzyme that generally confers resistance to several antibiotics, the most relevant ones being kanamycin, neomycin, paromycin, butirosin, gentamicin B and geneticin. In its opinion on the application for placing on the market of the genetically modified potato EH92-527-1, the GMO Panel of the European Food Safety Authority (EFSA) concluded that the use of *nptII* as a selection marker does not pose a risk to the environment or to human and animal health.

As indicated in his letter, the Commission representative is seeking confirmation from EMEA as to whether, notwithstanding the WHO classification, the current or possible uses of the antibiotics for which the *nptII* gene confers resistance are in line with the opinion of the GMO Panel of EFSA indicating that these antibiotics have no or only minor therapeutic relevance in human medicine and only restricted use in defined areas of veterinary medicine and, if not, whether the current or possible medicinal uses might have an impact on the conclusions of the EFSA GMO Panel.

In his response letter dated 6 February to Mr Robert Madelin, Dr Thomas Lönngren, the executive director of the EMEA commented that the scientific committeees of the EMEA would be able to comment comprehensively in relation to the issue of possible uses of these antibiotics in human and veterinary medicine. However, it was felt to be more appropriate for EFSA to possibly reconsider the conclusions of the panel in view of any new information provided by the EMEA scientific committees.

### CHMP and CVMP overall conclusions

The following is based on the assumption that the substrate specificity of the product of the *nptII* gene used as a marker in the potato in question is restricted to neomycin and kanamycin (and geneticin), as stated in the opinion published in the EFSA journal (2004) 48:1-18., and does not extend to gentamicin. This point is important due to different medical uses of these antibiotics.

1. Human medicines considerations

The therapeutic relevance of kanamycin and neomycin in human medicine has been addressed by the GMO panel of EFSA. The EMEA/CHMP can add the following points to that opinion. In summary these points consider a more long-term view recognising the potential development in the aminoglycoside class indicating that the role of these medicinal products might become increasingly relevant.

- As indicated in the report from the EFSA, Neomycin is indicated in important clinical conditions such as for example in hepatic encephalopathy.

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- Not withstanding the EFSA opinion, aminoglycosides is a class of antibiotics that has become increasingly important in the prevention and treatment of serious invasive bacterial infections in humans. This is because gram-negative bacteria (and tuberculosis bacteria) are becoming resistant to other classes of antibiotics. Consumption data from Sweden for example show a use of about 5.7 DDD (Defined daily doses) per 1000 inhabitants, or 0.02 DDD/1000 inhabitants and day in 2006, which indicates a 25% increased usage from 2002. In France the consumption is about 0.13-0.15 DDD/Day/1000 inhabitants and relatively stable since 2002[1]. Similar figures come from Estonia (personal communication).

- Although it is recognised that this marker gene only codes for resistance to kanamycin and neomycin the clinical/public health implications of this may not always remain the same. It is true that aminoglycosides and especially kanamycin and neomycin are used relatively infrequently and that the potential impact of this resistance gene therefore appears less relevant, at least in a short-term perspective. However, that situation may change as new chemical entities similar to kanamycin and neomycin could be developed. New chemical entities similar to kanamycin and neomycin could have other properties in relation to, for example, absorption from the gastrointestinal tract and with regard to side-effects. They thus have the potential to become extremely important to treat otherwise multi-resistant gram-negative infections and Tuberculosis.

- Aminoglycosides such as kanamycin are currently recommended for treatment in multidrug resistant tuberculosis (MDR-TB). Drug resistance in TB is part of the explanation for the resurgence of TB. WHO estimates that eight million people get TB every year. In the absence of an effective therapy, infectious MDR-TB patients will continue to spread the disease, producing new infections with MDR-TB strains. Until we introduce a new drug with demonstrated activity against MDR strains, this aspect of the TB epidemic could begin to explode at an exponential level (from the Global Alliance for TB Drug development (http://www.tballiance.org).

- In Estonia, Kanamycin was very recently introduced in the TB program (personal communication).

- The EMEA included kanamycin for potential use in MDR-TB in the case of bioterrorism (http://emea.europa.eu/pdfs/human/bioterror/11.Otherbacterial.pdf)

2. Veterinary usage consideration

The use of neomycin and kanamycin is currently limited, but this does not equate to "minor therapeutic importance". Importance is not measured by the quantity used, but rather relates to the need for the antibiotic and what alternatives exist, if any. As resistance continues to increase to the alternative drugs, the importance of neomycin and kanamycin and future derivatives of these drugs can be expected to increase, e.g. therapy of neonatal diarrhoea in piglets and treatment of multi-resistant enteric gram negative infections. Aminoglycosides, as a group, are a class of antibiotics critically important for veterinary medicine and animal production. The following aminoglicosides are part of veterinary medicines for food producing species in the EU; apramycin, dihydrostreptomycin, gentamicin, kanamycin, neomicin, paromomycin, spectinomycin and streptomycin.

3. Overall conclusions from Human and Veterinary

The Committees therefore concluded that neomycin, and kanamycin, are of importance for veterinary and human use and that their current and potential future use cannot be classified as of no or only minor therapeutic relevance.

The Committees considered that their area of competence does not extend to a detailed consideration of the likelihood of transfer of antibiotic resistance genes from plant material to bacteria of man and animals and they are not therefore in a position formally to comment on the EFSA conclusions that the likelihood

[1] Information obtained from Strama (www.strama.se) and Afssaps (personal communication).

and significance of such an event are extremely low. However, some observations on this issue and information on the use of the relevant antibiotics in animals and man are provided in Annex 1 and 2.

**Annex 1: Comment and information on the use of aminoglycoside antibiotics provided by the Scientific Advisory Group on Antimicrobials of the CVMP**

EFSA has evaluated the safety of the use of *nptII* as a maker gene in a modified potato line and has previously evaluated more generally the use of antibiotic resistance marker genes. EFSA considers that the use of *nptII* as a marker gene does not pose a risk for the environment or to animal, based on the following:

1. the probability of gene transfer from the GM plant to bacteria is possible but very low under natural circumstances

SAGAM noted that, transfer of nptII from plants to bacteria has been shown (Tepfer D, Garcia-Gonzales R, Mansouri H, Seruga M, Message B, Leach F, Perica MC. Homology-dependent DNA transfer from plants to a soil bacterium under laboratory conditions: implications in evolution and horizontal gene transfer. Transgenic Res. 2003 Aug;12(4):425-37.)

2. the gene nptII that is used as a marker gene confers resistance to neomycin, kanamycin and geneticin only, and not to gentamicin (otherwise normally expected for nptII).

This is crucial as the importance of gentamicin not only in human medicine, but also in veterinary medicine (e.g. for horses) is undisputed, and the following arguments refer to kanamycin and neomycin only.

In the opinion from 2004[2] (page 7), reference is given to two reviews from 1993 and 1994. The reference has not been located, and the CVMP/SAGAM cannot therefore assess the scientific basis for this point, nor the independence of the authors. *The following is based on the assumption that the substrate specificity of the product of the nptII gene used as marker in the potato in question is really restricted to neomycin and kanamycin (and geneticin)*

3. the use of kanamycin and neomycin in veterinary medicine is limited to certain conditions (enteritis in pigs and calves)

It is true that the main use of neomycin or kanamycin is for treatment of enteritis in young animals. This is one of the most common indications for use of antimicrobials in food-producing animals. According to DANMAP 2005, aminoglycosides were used orally in water for treatment of pigs in a quantity that corresponds to about 13% of the in water medication given to pigs. This use is mainly neomycin, thus the use is limited but not minor. Also, one should consider the alternatives; if neomycin is not used for these indications, other antibiotics like fluoroquinolones would need to be used.

*In the CVMP/SAGAM opinion, neomycin and kanamycin are valuable antibiotics for treatment of, e.g. E. coli associated enteric diseases in food-producing animals. The extent of use of neomycin/kanamycin to treat that condition will vary between countries, depending on what is available and on the occurrence of resistance to alternative antimicrobials.*

4. from point 3 & 4, the conclusion that neomycin & kanamycin is of "minor therapeutic importance" is drawn

The terms "infrequent use" and "limited indications" cannot be equated with "minor therapeutic importance". The use may remain infrequent, but the *importance* of use of neomycin/kanamycin for decolonisation/decontamination may well increase as a consequence of increasing problems with multiresistant or panresistant (ESBL producing) gram-negatives and of multiresistant staphylococci. This has already happened to colistin, long thought to be an old obsolete toxic drug with some minor

2 http://www.efsa.europa.eu/etc/medialib/efsa/science/gmo/gmo_opinions/384.Par.0001.File.dat/opinion_gmo_05_en1.pdf

uses in veterinary medicine. Colistin is today a life saving last resort treatment for infections with multiresistant Gram-negative bacteria in human hospitals.

5. neomycin/kanamycin resistance is already widespread

Occurrence of resistance to neomycin and kanamycin varies substantially between countries and bacterial species. Information on occurrence in *Salmonella* and *E. coli* is available in the EFSA Zoonosis report, 2005[3] "annex level 3".

**Importance of use in veterinary medicine of neomicin/kanamycin in some countries of the European Union**

The enclosed compilation is not exhaustive and comprises answers from experts on antimicrobial resistance and not necessarily that of the National Authorities.

Maximum Residue Levels (MRL) are available for the substances neomycin and kanamycin (http://www.emea.europa.eu/index/indexv1.htm), indicating that applicants consider them of sufficient value to apply for an MRL to permit their use in veterinary medicinal products for food producing species:

**France**: neomycin is used regularly for treatment of diarrhoea in pigs and is not a minor drug. The level of resistance varies between 5 and 20 % in *E. coli* samples in the French monitoring programme (see FARM report[4]). Sales of aminoglycosides in 2005 in France were 77.8 Tonnes (5.89% of total sales)[5].

**Denmark**: the use of aminoglycosides in piglets and calves in Denmark is almost exclusively restricted to neomycin.

**Germany**: the following number of products are licensed:

| | |
|---|---|
| Gentamicin: | Veterinary medicine 25 |
| Kanamycin: | Veterinary medicine 1 |
| Neomycin: | Veterinary medicine 30 |

**The Netherlands**: neomycin is used for oral treatment of enteritis in pigs and calves, for Bovine Respiratory disease by injection in combination with benzylpenicillin and for local treatment of mastitis (always in combined with a beta-lactam) and in eye and ear ointments. Specifically the parenteral use of neomycin-penicillin is substantial.

**Spain**: different Marketing Authorisations for veterinary medicinal products from different Laboratories, which include gentamicin or neomycin in its composition, are available. No kanamycin, neither paromycin, butiroxin nor geneticin is available.

**Sweden**: The above-mentioned aminoglycosides are not authorised for animals in Sweden.

In Ireland kanamycin is used in the treatment of mastitis in cows.

**OIE list of Veterinary Critically Important Antimicrobials (VCIA)**

Reference is made on the request from the Commission to the WHO list of critically important antimicrobials. We would like to highlight that kanamycin and neomicin are included in the OIE list of VCIA. For aminoglycosides the following is indicated:

***"Importance of aminoglycosides***

[3] http://www.efsa.europa.eu/en/science/monitoring_zoonoses/reports/1277.html
[4] FARM 2003-2004, French antimicrobial resistance monitoring in bacteria of animal origin, afssa
[5] http://www.anmv.afssa.fr/documents/rapport2005_final-antibio.pdf

*The diseases controlled by aminoglycosides, either alone or in combination, are particularly debilitating to young animals and failure to adequately treat outbreaks would result in much suffering among affected animals. Similarly, the enteric infections affecting pigs and calves are effectively and economically treated orally with aminoglycosides, either alone or in combination. The wide range of applications and the nature of the diseases treated make aminoglycosides critically important for veterinary medicine and animal production."*

The use of aminoglycosides in routine veterinary therapy is well established as illustrated by standard text books, such as: "Antimicrobial Therapy in Veterinary Medicine, third edition, Edited by J F. Prescott et al."

**Annex 2**: Information on human consumption from some EU countries

<table>
<tr><th>Country</th><th>Information on consumption</th></tr>
<tr><td>Sweden</td><td>See main text<br>Aminoglycosides<br>2002: 4.56 ddd/1000/year; 2003: 4.78 2004: 5.16; 2005: 5.32; 2006: 5.75<br>Kanamycin and Neomycin not licensed.</td></tr>
<tr><td>France</td><td>See main text<br>Aminoglycosides: 2002: 0.15 ddd/1000/day; 2003: 0.12; 2004: 0.13; 2005: 0.13. Kanamaycin not licensed. Neomycin licensed.</td></tr>
<tr><td>Italy</td><td>Kanamycin not licensed. Neomycin licensed. The hepatic encephalopathy indication was recognised by Italian experts.</td></tr>
<tr><td>Germany</td><td>The following number of products are licensed<br><br>Gentamicin: Human medicine 80<br>Kanamycin: Human medicine 9<br>Neomycin: Human medicine 44</td></tr>
<tr><td>Lithuania</td><td>Kanamicin data are available in DDD/1000 persons/per day while Neomicin in packs only:
<table>
<tr><th></th><th>IQ</th><th>IQ</th><th>IQ</th></tr>
<tr><td>Kanamicin</td><td>0.98</td><td>0.65</td><td>2.93</td></tr>
<tr><td>Neomicin (sold as combination products)</td><td></td><td></td><td></td></tr>
<tr><td>Maxitrol eye drops (in packs)</td><td>2608</td><td>4298</td><td>4514</td></tr>
<tr><td>Maxitrol eye ointment (in packs)</td><td>834</td><td>2095</td><td>1853</td></tr>
<tr><td>Polygynax</td><td>8958</td><td>18050</td><td>20516</td></tr>
<tr><td>Dexona eye drops</td><td>17803</td><td>73733</td><td>73052</td></tr>
</table></td></tr>
<tr><td>Estonia</td><td>Estonia has neomycin topicals authorised (ointment, cream, eye drops, tablets for oral mucosal infections) and parenteral gentamicin as well (use in 2005 was 0,22 DDD/1000/day). Kanamycin was very recently used in the TB program and most probably still is, this gets imported for the tb program, variant of named pt basis.</td></tr>
</table>

European Food Safety Authority

# Statement of the Scientific Panel on Genetically Modified Organisms on the safe use of the *npt*II antibiotic resistance marker gene in genetically modified plants

**adopted on 22-23 March 2007**

## 1. BACKGROUND

The Commission is currently considering the authorisation for placing on the market of the genetically modified (GM) potato line EH92-527-1 under Regulation (EC) No 1829/2003 on GM food and feed and under Directive 2001/18/EC, part C. The GM potato, developed for amylopectin production, also contains a *npt*II gene used as a selectable marker. The *npt*II gene codes for an aminoglycoside phosphotransferase conferring resistance to antibiotics such as kanamycin, neomycin, paromomycin, butirosin, gentamycin B and geneticin.

Directive 2001/18/EC (EC, 2001) states that Member States and the Commission shall ensure that GMOs which contain genes expressing resistance to antibiotics in use for medical or veterinary treatment are taken into particular consideration when carrying out an environmental risk assessment. This is with a view to identify and phase out antibiotic resistance marker genes (ARMGs) in GMOs which may have adverse effects on human health and the environment.

Over the last years, the use of antibiotic resistance marker genes for selection of GM plants, and which have been subject of safety assessment under Part C of the Directive 2001/18/EC, has been limited to the *npt*II gene. Some applications of GM plants submitted under Regulation No 1829/2003 also include the use of the *npt*II gene as a selectable marker, while in other cases the *npt*II gene has been excised after selection, or other markers such as the *epsps* and *pat* genes coding for herbicide tolerance were used. No other antibiotic resistance marker genes are currently present in applications submitted for approval.

According to an earlier conclusion of the Scientific Panel on Genetically Modified Organisms (GMO Panel) (EFSA, 2004)[1] the use of *npt*II as a selectable marker in genetically modified plants and, more specifically, in the potato line EH92-527-1 (EFSA, 2006), does not pose a risk to the environment or to human and animal health. This conclusion was based on the low probability of gene transfer from plants to bacteria, the already widespread presence of the *npt*II gene in bacterial populations, and the limited use of kanamycin and neomycin in human and veterinary medicine.

The Commission sought confirmation from the European Medicines Agency (EMEA) as to whether, notwithstanding a WHO working group classification of aminoglycosides as critically important antibacterials (WHO, 2005), the current or possible future uses of the antibiotics for which the *npt*II gene

[1] http://www.efsa.europa.eu/etc/medialib/efsa/science/gmo/gmo_opinions/384.Par.0001.File.dat/opinion_gmo_05_en1.pdf

confers resistance is still in line with the earlier EFSA opinion. The EMEA was asked to consider whether the current or possible future medicinal uses of these antibiotics might have an impact on the earlier conclusions of the GMO Panel.

In response to the Commission's request, the EMEA indicated that aminoglycosides comprise a class of antibiotics that has become increasingly important in the prevention and treatment of serious invasive bacterial infections in humans, since Gram-negative bacteria (and tuberculosis bacteria) are becoming resistant to other classes of antibiotics. The EMEA also stressed that, although kanamycin and neomycin are used relatively infrequently, the potential development of new chemical entities similar to kanamycin and neomycin should also be taken into account. In addition, although the veterinary use of kanamycin and neomycin is currently limited, aminoglycosides as a group are a class of antibiotics critically important for veterinary medicine.

The EMEA considered that its competence did not extend to a detailed consideration of the likelihood of gene transfer of antibiotic resistance genes from plant material to bacteria of man and animals.

Subsequently, the Commission requested EFSA (letter dated March 2, 2007) to consider the information provided by the EMEA and to indicate the potential consequences of the EMEA's conclusions on the safety assessment of the *npt*II gene and, where applicable, on the specific assessments of GMOs and derived food and feed.

## 2. ASSESSMENT

A concern with respect to the presence of antibiotic resistance marker genes in GM plants is the potential for increased resistance to antibiotics in humans, animals and in organisms in the wider environment as a result of horizontal gene transfer. The safety assessment of the GMO Panel concerning the presence of the *npt*II gene in GM plants builds on a number of considerations. Key elements are the very low likelihood of transfer of a functional *npt*II gene (or any other gene), from GM plant material to microorganisms, and the prevalence of the *npt*II gene in bacterial clinical isolates and in the environment.

### *2.1. Likelihood of transfer of the* nptII *gene from the genome of GM plants to bacteria*

In considering the probability of functional gene transfer from plants into bacteria in the environment or human/animal gut, several aspects need to be taken into account:

(i) DNA is released from plant material by normal digestion processes that take place in the gastrointestinal tract, or by activities of nucleases present in various organisms in the environment.

(ii) The probability that bacteria will be exposed to DNA stretches long enough to contain the intact *npt*II gene is very low because of the above mentioned digestion and degradation processes (Lorenz and Wackernagel, 1994).

(iii) The *npt*II gene from plant material can only be taken up by competent bacteria via natural transformation, a process that occurs infrequently in many bacteria and in most environmental conditions (Davison, 1999).

(iv) If the intact *nptII* gene enters the bacteria, it will be rapidly degraded by restriction endonucleases in many bacterial cells which possess DNA restriction systems in order to destroy foreign DNA (Davison, 1999).

(v) If the intact *nptII* gene does indeed survive, the probability of its incorporation into the bacterial genome is very low unless there are homologous regions already present in the bacterial genome. Gene transfer from plants to bacteria has only been demonstrated under laboratory conditions when regions of homology were already present in the recipient bacterium (Bennett et al., 2004, de Vries et al., 2001, de Vries and Wackernagel, 2002, Kay et al., 2002, Tepfer et al., 2003) .

(vi) Expression of the incorporated *nptII* gene is unlikely considering that in GM plant material the *nptII* gene is under the control of a promoter with preferential expression in plants, which does not support its efficient expression in bacteria.

(vii) Stable integration and inheritance of the *nptII* gene in the host bacterium is not likely in the absence of selective pressure from a relevant antibiotic.

When all of the above mentioned aspects are taken into account, the probability of functional gene transfer from plants into microorganisms is extremely low. It is not surprising that transfer of an antibiotic resistance marker from GM plants to bacteria has not been observed under natural conditions (Gay and Gillespie, 2005).

The EMEA has indicated that under laboratory conditions gene transfer from plants to bacteria has been demonstrated. EFSA has addressed this issue more extensively in its Opinion of 2004 (section 4) (EFSA, 2004). Gene transfer from plants to bacteria has only been demonstrated in a few highly transformable bacterial species (e.g., *Acinetobacter* sp. BD413 or *Pseudomonas stutzeri*) under artificial and forced laboratory conditions when regions of homology were already present in the recipient bacterium (Bennett et al., 2004, de Vries et al., 2001, de Vries and Wackernagel, 2002, Kay et al., 2002, Tepfer et al., 2003). In the absence of this optimisation of the process and selection pressure, resistance gene transfer from GM plants to bacteria, even in the laboratory, could not be demonstrated (Gebhard and Smalla, 1998).

### *2.2. Prevalence of the nptII gene in soil, humans and animals*

As indicated in the Opinion (of the GMO Panel) on the use of antibiotic resistance genes as markers in GM plants, antibiotic resistance is a common feature in natural microbial communities in soils, aquatic systems, and habitats associated with animals and humans (EFSA, 2004).

There is already a widespread presence of *nptII* in the soil environment as evidenced from DNA-based work with *nptII* as a probe in different locations in Western Europe (NSCFFS, 2005, Smalla et al., 1993) and in the USA (Leff et al., 1993).

Studies indicate that, as expected of a gene located on a transposable genetic element, *nptII* is located on a wide range of replicons in bacterial clinical isolates from humans (Alvarez and Mendoza, 1992, Chang et al., 1992, Flamm et al., 1993). The *nptII* gene was present in 2.5% of bacterial clinical isolates resistant to kanamycin and neomycin collected between 1987 and 1991 in several European and Central and South American countries (Shaw et al., 1993). Studies on the prevalence of the *nptII* gene in animal-associated bacterial populations have not been found in the scientific literature.

### *2.3. Contribution of the* nptII *gene to the prevalence of resistance to kanamycin*

Kanamycin-resistant bacteria are ubiquitous in nature. Selective plating of different environmental samples on kanamycin-containing medium reduced the microbial count from $10^7$ to $10^4$ CFU/g (Smalla and van Elsas, 1996, Smalla et al., 1993). Only a fraction of kanamycin-resistant bacteria contain the *npt*II (*aph(3')-IIa*) gene, the other resistant bacteria having different genes and/or other mechanisms conferring kanamycin resistance. The *npt*II gene has been reported to occur naturally only in eubacteria. In one survey, 3 out of 184 kanamycin resistant bacterial isolates from three stream sites in the USA (Leff et al., 1993) and 44 out of 355 from different habitats in the Netherlands (Smalla et al., 1993) contained *npt*II sequences.

### *2.4. Potential mutations of the* nptII *gene resulting in resistance to other antibiotics*

As reported in the opinion of the GMO Panel on antibiotic resistance genes as markers in GM plants (EFSA, 2004), resistance towards amikacin, an important reserve antibiotic could be obtained under laboratory conditions and was the result of a mutated *npt*II gene and a diminished rate of amikacin uptake into the bacterial cell (Perlin and Lerner, 1986). The increased affinity of a mutated *npt*II gene product for amikacin was later confirmed by site-directed mutagenesis which resulted in one altered nucleotide in the gene and an eight-fold increase in amikacin resistance in *E.coli* (Kocabiyik and Perlin, 1992). It has been suggested that the increased affinity for amikacin conferred by this mutation, might impair the clinical effectiveness of the drug. However, to date no clinical amikacin resistant strains with a mutated *npt*II gene have been identified.

## 3. CONCLUSIONS

The GMO Panel agrees with the EMEA that the preservation of the therapeutic potential of the aminoglycoside group of antibiotics is important. The Panel is also of the opinion that the therapeutic effect of these antibiotics will not be compromised by the presence of the *npt*II gene in GM plants, given the extremely low probability of gene transfer from plants to bacteria and its subsequent expression. Furthermore, the GMO Panel considers it very unlikely that the presence of the *npt*II gene in GM plants will change the existing widespread prevalence of this antibiotic resistance gene in bacterial sources in the environment. The GMO Panel also points to evidence which indicates that integration of the *npt*II gene would only be one of many mechanisms by which bacteria could become resistant to aminoglycosides such as kanamycin.

Therefore, the GMO Panel reiterates its earlier conclusions (EFSA, 2004) that the use of the *npt*II gene as selectable marker in GM plants (and derived food or feed) does not pose a risk to human or animal health or to the environment. The GMO Panel also confirms earlier safety assessments of GM plants and derived food/feed comprising the *npt*II gene.

The GMO Panel emphasizes that the use of antibiotic resistance marker genes in GM plants has been the subject of several reviews (Gay and Gillespie, 2005, Goldstein et al., 2005, Miki and McHugh, 2004, Nap et al., 1992, Nielsen et al., 1998, Ramessar et al., 2007) and expert consultations: Working Party of the British Society for Antimicrobial Chemotherapy (Bennett et al., 2004), FAO/WHO Consultation on Foods Derived from Biotechnology (FAO/WHO, 2000), Scientific Steering Committee of the European Commission (SSC, 1999) Zentrale Kommission für die Biologische Sicherheit, DE (ZKBS, 1999), The Advisory Committee on

Novel Foods and Processes, UK (ACNFP, 1996). It has been concluded in these reports that the frequencies of gene transfer from plants to bacteria are likely to be extremely low and that the presence of antibiotic resistance marker genes, and in particular the *npt*II gene, in GM plants do not pose a relevant risk to human or animal health or to the environment.

## DOCUMENTATION PROVIDED TO EFSA

1. Letter from DG SANCO, dated 2 March 2007, concerning the presence of the *npt*II resistance gene in genetically modified organisms (ref. SANCO/E1/SG/cc (2007)D/510137).

2. Document from the EMEA Committee for Medicinal Products for Veterinary Use and Committee for Medicinal Products for Human Use, dated 22 February 2007, entitled "Presence of the antibiotic resistance marker gene nptII in GM plants for food and feed uses", (ref. EMEA/CVMP/56937/2007-Final).

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## Scientific Panel Members

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## Acknowledgement

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**Ministeriet for Fødevarer, Landbrug og Fiskeri**
Departementet

Folketingets Udvalg for Fødevarer, Landbrug
og Fiskeri

Den 11. marts 2008
Sagsnr.: 39

./. Vedlagt fremsendes til udvalgets orientering svar på spm. 1 (alm.del. 2849 – landbrug og fiskeri) fra Folketingets Europaudvalg vedrørende antibiotikaresistente genmarkører i GMO'er, der også bruges i behandling.

Med venlig hilsen

Marie Louise Flach de Neergaard

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**Ministeriet for Fødevarer, Landbrug og Fiskeri**

Folketingets Europaudvalget

København, den
FVM 514

Folketingets Europaudvalg har i brev af 12. februar 2008 (Alm. del – 2849 – landbrug og fiskeri spørgsmål nr. 1) udbedt sig min besvarelse af følgende:

**Spørgsmål 1:**
"WHO anbefaler, at man ikke anvender antibiotikaresistente genmarkører i GMO'er, når det handler om resistensgener, der også bruges i behandlingen af mennesker og dyr. De nævnte markører anvendes ifølge Greenpeace netop i behandlingen af mennesker og dyr, jf. KOM (2007) 0814, KOM (2007) 0815, KOM (2007) 0816 og KOM (2007) 0813. Ministeren bedes, som lovet på europaudvalgsmødet den 8. februar 2008, af- eller bekræfte, at netop disse typer af antibiotika i stigende grad bruges i Sverige (en stigning på 25 % siden 2002) og er vigtige i behandlingen af tuberkulose."

**Svar:**
Statens Serum Institut er anmodet om bidrag til besvarelse af ovennævnte spørgsmål, som jeg henviser til.

Statens Serum Institut oplyser følgende: " Statens Serum Institut har ikke haft stillet de anførte henvisninger til rådighed, men forudsætter med baggrund i tidligere spørgsmål fra Europaudvalget, at der henvises til resistensgenet NPTII. Dette er et enzym, der kan inaktivere visse aminoglykosider, der er en gruppebetegnelse for en række antibiotika, hvor af nogle har større betydning end andre ift. human behandling.

Så vidt Statens Serum Institut har kunnet erfare, er der i Sverige sket en stigning på sygehuse i anvendelsen af aminoglykosider (JO1 GB) på 2,9 DDD/100 indlæggelser i 2002 til 3,3 DDD/ 100 indlæggelser i 2005 (Swedres 2006, A Report on Swedish Antibiotic Utilisation and Resistance in Human Medicine, SMI, Stockholm, ISSN 1400-3473). Det er ikke opgivet, om stigningen relaterer sig til bestemte undertyper.

De anførte antibiotika er ikke første valg ved behandling af tuberkulose i Danmark, men kan finde anvendelse ved bivirkninger overfor andre stoffer og ved resistent

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tuberkulose. I andre lande med højere forekomst af tuberkulose, herunder resistent tuberkulose, vil disse antibiotika kunne spille en mere fremtrædende rolle i en effektiv behandling."

# Ministeriet for Fødevarer, Landbrug og Fiskeri

Folketingets Udvalg for Fødevarer,
Landbrug og Fiskeri

København, den 14. marts 2008
Sagsnr.: 11260

Udvalget for Fødevarer, Landbrug og Fiskeri
(2. samling)
FLF alm. del - Svar på Spørgsmål 157 og 158
Offentligt

Folketingets Udvalg for Fødevarer, Landbrug og Fiskeri har i skrivelse af 27. februar 2008 (Alm. del - spørgsmål nr. 157) udbedt sig min besvarelse af følgende:

**Spørgsmål 157:**

"Vil ministeren i forlængelse af ministerens svar på FLF alm. del – samrådsspm. N om fire antibiotikaresistente GMO'er den 27. februar 2008 oversende det talepapir, der lå til grund for ministerens besvarelse?"

**Svar:**
Vedlagt fremsendes talepapiret i forbindelse med samrådet den 27. februar 2008.

Eva Kjer Hansen

/Jakob Møgelvang

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**Ministeriet for Fødevarer, Landbrug og Fiskeri**

Den 26. februar 2008

**FLF Alm. del,**
**samrådsspm. N**

# TALEPUNKT

**DET TALTE ORD GÆLDER**

**Vedr. FLF alm. del, samrådsspørgsmål N:**
**Hvordan vil ministeren sikre, at de fire antibiotikaresistente gmo'er, som Danmark stemte imod godkendelsen af på ministerrådsmødet den 18. februar 2008, ikke bliver markedsført i Danmark?**

- Spørgsmålet relaterer sig til den igangværende EU-godkendelsesprocedure vedrørende tre genmodificerede majskrydsninger, samt en genmodificeret stivelseskartoffel i henhold til GMO-forordningen (forordning (EU) 1829/2003)

- Det drejer sig om godkendelse af:
- MON863xMON810-majs,
- MON863xNK603-majs,
- MON863xMON810xNK603-majs og
- EH92-527-1 kartoffel

- Ved drøftelserne i Europaudvalget den 8. februar 2008 udtrykte flere partier bekymring for sikkerheden af gmo'erne, idet der er indsat et antibiotikaresistens-markør (ARM)-gen nptII.

- Der kunne derfor ikke opnås flertal for dansk støtte til forslagene om godkendelse af disse fire GMO'er, hvorfor Danmark

på rådsmødet den 18.-19. februar 2008 stemte imod godkendelserne.

- Spørgsmålet er nu, hvordan det kan sikres, at de fire antibiotikaresistente gmo'er, ikke bliver markedsført i Danmark.

- Hertil må jeg svare, at såfremt de fire gmo'er bliver godkendt ved en kommissionsbeslutning, vil denne beslutning være umiddelbart gældende i alle medlemsstater, herunder i Danmark.

- Beslutningen om godkendelse vil være baseret på udtalelser fra EFSA, som vurderer, at der ikke er nogen risiko for menneskers eller dyrs sundhed eller for miljøet ved det anvendte nptII-gen.

- De danske eksperter ved Fødevareinstituttet har udtalt, at de er enige i EFSA's vurdering.

- Der er således ikke noget retsligt grundlag for at indføre et nationalt forbud.

**Ministeriet for Fødevarer, Landbrug og Fiskeri**

Folketingets Udvalg for Fødevarer,
Landbrug og Fiskeri

København, den 14. marts 2008
Sagsnr.: 11262

Folketingets Udvalg for Fødevarer, Landbrug og Fiskeri har i skrivelse af 27. februar 2008 (Alm. del - spørgsmål nr. 158) udbedt sig min besvarelse af følgende:

**Spørgsmål 158:**

"Vil ministeren i forlængelse af ministerens svar på FLF alm. del – samrådsspm. N om fire antibiotikaresistente GMO'er den 27. februar 2008 redegøre for sammensætningen af EFSA?"

**Svar:**
Jeg forstår spørgsmålet således, at der menes sammensætningen af EFSA's GMO-panel. Hertil kan jeg oplyse, at GMO-panelet består af 21 uafhængige videnskabelige eksperter fra et bredt udsnit af EU's medlemslande. Eksperterne udvælges på baggrund af deres særlige ekspertise vedrørende risikovurdering af GMO'er. Medlemmerne af panelet udpeges af EFSA's bestyrelse for tre år af gangen.

På EFSA's hjemmeside: http://www.efsa.europa.eu findes der en beskrivelse af de enkelte medlemmer af EFSA's GMO-panel.

Eva Kjer Hansen

/Jakob Møgelvang

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# Ministeriet for Fødevarer, Landbrug og Fiskeri

Folketingets Udvalg for Fødevarer,
Landbrug og Fiskeri

København, den 14. marts 2008
Sagsnr.: 11263

**Udvalget for Fødevarer, Landbrug og Fiskeri**
**(2. samling)**
**FLF alm. del - Svar på Spørgsmål 159**
**Offentligt**

Folketingets Udvalg for Fødevarer, Landbrug og Fiskeri har i skrivelse af 27. februar 2008 (Alm. del - spørgsmål nr. 159) udbedt sig min besvarelse af følgende:

**Spørgsmål 159:**

"Vil ministeren i forlængelse af ministerens svar på FLF alm. del – samrådsspm. N om fire antibiotikaresistente GMO'er den 27. februar 2008 oplyse, hvilke initiativer ministeren vil tage for at ændre EFSA's gruppeopdeling af gener?"

**Svar:**
Jeg kan oplyse, at jeg sammen med miljøministeren har skrevet til Europa-Kommissionen og anmodet om en nærmere redegørelse for den gruppeinddeling af antibiotika resistens markørgener, som EFSA foretog i 2004 og hvorvidt der er behov for en revidering af denne klassificering.

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# Risikovurdering af GMO

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Afd. for Risikovurdering og Toksikologi

# Retningslinier for sundhedsmæssig risikovurdering af GMO

**WHO/FAO**

**OECD**

**NORDISK**

**CODEX**

**ILSI**

**SCF**

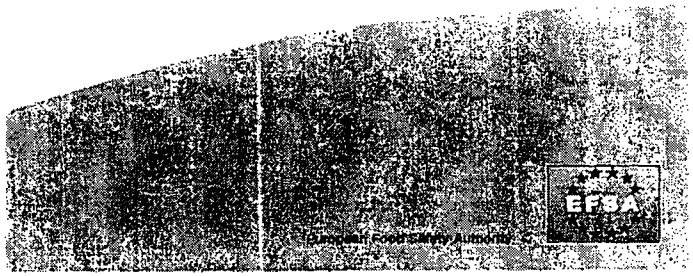
**EFSA**

# EFSA retningslinier for risikovurdering af GMO

GUIDANCE DOCUMENT
OF THE SCIENTIFIC PANEL
ON GENETICALLY MODIFIED
ORGANISMS FOR THE RISK
ASSESSMENT OF GENETICALLY
MODIFIED PLANTS AND
DERIVED FOOD AND FEED

Adopted on 24 September 2004
Updated on 7 December 2005
Final, edited version of 20 April 2006

May 2006




Fødevareinstituttet

# SUNDHEDSRISICI ?

**NÆRINGSVÆRDI**

**GIFTIGE STOFFER**

**ALLERGENER**

**GENOVERFØRSEL (antibiotika resistens)**

**Direkte eller indirekte effekt som følge af gensplejsningen.**

# Substantial Equivalence
# OECD 1993

**"the concept of substantial equivalence embodies the idea that existing organisms used as food or as a source of food can be used as the basis for comparison when assessing the safety of the human consumption of a food or food component that has been modified or is new"**

# Trin 1 - Konstruktion

**På første trin vurderes selve metoden og resultatet af gensplejsningen på DNA-niveau herunder:**

- **Indsatte gener**
- **Forventet effekt afhængig/uafhængig**
- **Stabilitet, ekspression**

# Sammenlignende undersøgelser

?

=

# Forslag til analyser ved sammenlignende undersøgelser af majs. (OECD konsensus dokument.)

| Parameter | Olie | Stivelse | Mel | Kerner |
|---|---|---|---|---|
| Proximate analyser[a] | | X | X | X |
| Mineraler | | | | X |
| Vitaminer | | | | X |
| Aminosyrer | | | (X) | X |
| Fedtsyrer | X | | X | X |
| Phytin syre | | | | X |
| Raffinose | | | | X |
| Furfural | | | | X |
| Ferulin syre | | | | X |
| p-coumarin syre | | | | X |

a: Proximate includes protein, fedt, fibre, aske og kulhydrater

# Trin 2 – eksempel fortsat
# MON89788 sojabønne

**Analyser i alt 475**

**Antal forventede forskelle af tilfældige årsager 24**

**Antal fundet ved 95% sikkerhed: 36**

**Fleste forskelle relateres kun til en enkelt lokalitet.**

**Konklusion:** **Forskel – kan ikke udelukkes**

**Risiko – som anden majs**

# Antibiotika-resistens-gener
# ARM

- **Kan genet overføres til mikroorganismer?**
  - **Ikke påvist**
  - **worst case : ny kan res. bakterie for hver 750 mia eller 10 mill resistente i hhv tarm eller jord**

- **Kan enzymet NPTII kompromittere anvendelsen af kanamycin?**
  - **ATP krav**
  - **kanamycin giftigt (begrænset oral anvendelse)**

# Fordeling på egenskaber
# Kilde ISAAA 2006

| Egenskab | Areal (mill. ha) | Andel % |
|---|---|---|
| Herbicid tol. | 69,9 | 68 |
| Bt insekt res. | 19,0 | 19 |
| Begge | 13,1 | 13 |

# Fordeling på egenskaber majs EFSA ansøgninger

| Egenskab | antal | Markør |
|---|---|---|
| Herbicid tol. | 3 | - |
| Bt insekt res. | 4 | 2 (nptII+pmi) |
| Begge | 5 | - (amp) |
| Andet | 2 | 1 (pmi) |

Antibiotikaresistens-genmarkører i GMO'er - NPTII:

Der nævnes vedr. gmo ofte resistensgenet, NPTII. Dette er en forkortelse for enzymet: neomycin phosphotransferase II. Det er senere i litteraturen benævnt: aminoglycosid-3'-phosphotransferase II (APH(3')II). Dette refererer altså til en aminoglykosid-resistens markør, dvs et enzym, der kan inaktivere visse aminoglykosider, der er en gruppebetegnelse for en række antibiotika, hvoraf flere har været – eller stadig anvendes både til behandling af infektioner hos mennesker og dyr, samt til andre applikationer (f.eks. laboratoriebrug). NPTII har netop været anvendt til genetisk modificering af planteceller, da det koder for resistens over for et stof, der hedder geneticin, som åbenbart har kunnet anvendes i forbindelse med at finde de planteceller, der har fået indsat et ønsket gen.
APH(3')II er et af en række aminoglykosid phosphotransferaser, der er klassificeret efter deres angrebspunkt på aminoglykosid-molekylet , og efter hvilke aminoglykosider, de derfor inaktiverer, samt visse andre kriterier. APH(3') kan phosphorylere en OH-gruppe, der sidder på 3'-positionen på aminoglykosidmolekylet – og dermed inaktivere det, dvs at det ikke mere virker, eller kun dårligt, på bakterier. Kun aminoglykosider, der har en OH-gruppe siddende der, kan inaktiveres af enzymet, og det gælder bl.a. for kanamycin- og neomycin derivaterne. Kanamycin er et af de ældste aminoglykosider (det første var streptomycin), som senere blev stamfader til en længere serie af mere aktive aminoglykosider, kanamycin-derivater. De klinisk vigtigste – humant set - har været tobramycin og amikacin, der stadig anvendes udbredt – men i varierende grad – i Verden. Tobramycin anvendes i Danmark kun nu i mindre grad, nemlig til inhalationsterapi på patienter med Pseudomonas aeruginosa infektioner i luftvejene, hvilket overvejende er patienter med cystisk fibrose. Amikacin har været – men er ikke mere markedsført i Danmark. Det blev formentlig taget af markedet på grund af for lille salg, idet vi i Danmark i de sidste 30 år pga de gode (~ lave) resistensforhold har kunnet klare os med det noget billigere Gentamicin. Amikacin anses dog for et vigtigt aminoglykosid, fordi det er relativt stabilt over for de fleste aminoglykosid resistensmarkører og kan anvendes mod mange gentamicin-resistente bakterier.
APH(3')II har lidt forskellig virkning efter hvilken, mikroorganisme det befinder sig i, hvilket øger til forvirring på området – lige som den varierende klassifikation af genmarkøren. Det findes kromosomalt hos nogle Pseudomonas aeruginosa stammer, og er beskrevet på et plasmid i Stenotrophomonas maltophilia. I sidstnævnte bakterie medførte genet mindre følsomhed (~højere MIC-værdier) over for kanamycin, neomycin, paromomycin, butyrosin samt amikacin og tobramycin. Hos Pseudomonas aeruginosa er enzymet nævnt som givende nedsat aktivitet over for kanamycin og neomycin.
Kanamycin anvendes ikke mere til behandling af mennesker. Neomycin findes i visse hudpræparater (i Danmark), og her været anvendt indlejret i gaze til brug ved sårbehandling, samt har tidligere været brugt til peroral tarmdesinfektion f.eks. før tarmkirugi. Ingen af disse to antibiotika kan dog siges at have større betydning for human behandling, bl.a. var de relativt toxiske ved parenteral indgift. Amikacin derimod er et uhyre vigtigt humant antibiotikum, og resistensudvikling mod dette stof er uønsket.

Litteratur:
Fuchs et al. Bio/Technology 1993, 11: 1537-42.
Okazaki et al. Antimicrob Ag Chemother, 2007, 51: 359-360.
Hächler et al. Antimicrob Ag Chemother, 1996, 40: 1254-56.
Wrigth et al. Frontiers in Bioscience, 1999, 4, d9-21.

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## 1 Bekendtgørelse 1319, §3 resultat af folketingsforhandling.

§ 3. Der meddeles ikke godkendelse til forsøgsudsætning eller markedsføring af genetisk modificerede organismer, der indeholder gener, som giver resistens over for antibiotika, der anvendes i human- eller veterinærmedicinsk behandling.
*https://www.retsinformation.dk/Forms/R0710.aspx?id=12977*

Connie Hedegaard: Dansk ARM-forbud er for vidtgående ifht EU, regeringen er derfor ikke bundet af forbuddet i bekendtgørelse 1319. Dansk bekendtgørelse bør laves om så det bliver lovligt at godkende GMO med ARM der berører behandlingsmedicin.

## 2 Det der står i EU-loven er:

Artikel 4(2) i udsætningsdirektivet 2001/18:
"Medlemsstaterne og Kommissionen sikrer, at GMO'er, der indeholder gener, som udtrykker resistens over for antibiotika anvendt i human- eller veterinærmedicinsk behandling, tages specielt i betragtning ved miljørisikovurderingen med henblik på identifikation og udfasning af antibiotikaresistensmarkører i GMO'er, der kan have uønskede virkninger på menneskers sundhed og miljøet. Denne udfasning skal finde sted inden 31. december 2004 for så vidt angår GMO'er, der markedsføres i henhold til del C, og inden 31. december 2008 for så vidt angår GMO'er, der er tilladt i henhold til del B."

To læsninger: (A) at der faktisk menes en udfasning af alle ARM der berører behandlingsmedicin pga risiko for uønsket virkning, eller (B) at der ikke menes udfasning fordi der kan være ARM der berører behandlingsmedicin, uden at have uønskede virkninger på menneskers sundhed og miljø(?)

## 3 EU-Komissionens forståelse af ARM-forbuddet

Bruxelles, den 16.05.2000, KOM(2000)293 endelig, ,1998/0072 (COD)
UDTALELSE FRA KOMMISSIONEN
i henhold til EF-traktatens artikel 251, stk. 2, litra c), om Europa-Parlamentets ændringerne til Rådets fælles holdning til forslag til EUROPA-PARLAMENTETS OG RÅDETS DIREKTIV om udsætning i miljøet af genetisk modificerede organismer og om ophævelse af Rådets direktiv 90/220/EØF

...

Side 4-5
Med ændringsforslag 48 indføres (i artikel 4, stk. 2) år 2005 som frist for udfasning af markørgener for antibiotikaresistens. Kommissionen mener, at antibiotikaresistensmar-kørgener skal udfases og erstattes med alternativer så hurtigt, det er praktisk muligt. Der tales også om udfasning i den fælles holdning, og Kommissionen kan gå med til at skærpe dette politiske budskab. Det synes imidlertid ikke at være tilrådeligt at fastsætte en frist for udfasning af anvendelsen af disse markører. I denne forbindelse vil Kommissionen også foretrække, at der skelnes mellem forskningsaktiviteter og markedsføring af GMO'er. Inden for disse grænser kan ændringsforslag 48 derfor accepteres i princippet.
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2000:0293:FIN:DA:PDF

## 4 Danske regerings forståelse af ARM-forbuddet

L 131 (som fremsat): Forslag til lov om ændring af lov om miljø og genteknologi. (Gennemførelse af det nye udsætningsdirektiv m.v.). Fremsat den 28. februar 2002 af miljøministeren (Hans Christian Schmidt). Forslag til Lov om ændring af lov om miljø og genteknologi(Gennemførelse af det nye udsætningsdirektiv m.v.)

Hovedindholdet af det nye udsætningsdirektiv
Det nye udsætningsdirektiv er vedtaget med hjemmel i art. 95. Det nye udsætningsdirektiv forudsætter fuld harmonisering i medlemslandene. De væsentligste ændringer i det nye udsætningsdirektiv er;
...
– at de genetisk modificerede organismer, der indeholder gener, som giver resistens over for antibiotika, der anvendes i human og veterinærmedicin, skal udfases inden udgangen af 2004, når det gælder markedsførte produkter og inden 2008 for genetisk modificerede organismer til forsøgsudsætninger, http://www.folketinget.dk/Samling/20012/lovforslag_som_fremsat/L131.htm

Altså, EU loven skal tydeligvis forstås som den dengang blev forstået og er skrevet (læsning A i pkt 2).
Udfasning af ARM der berører behandlingsmedicin.
DK bekendtgørelses ikke et generelt forbud – omfatter kun ARM der anvendes i behandling. Der anvendes ifølge VetStat ca.5 tons Neomycin i dansk landbrug.

## 5 WHO/FAOs Codex Allimentarius (basis for WTO)

*CODEX Guideline for the conduct of Food Safety Assessment of Foods derived from recombinant-DNA plants", Section 5 – Other Considerations:*
*...58. Antibiotic resistance genes used in food production that encode resistance to clinically used antibiotics should not be present in foods."*

## 6 Beskyttelsesklausulen. Udsætningsdirektivet 2001/18, artikel 23(1)

Hvis en medlemsstat som følge af nye eller supplerende oplysninger, der er fremkommet efter, at tilladelsen er givet, og som påvirker miljørisikovurderingen, eller som følge af revurdering af eksisterende oplysninger på grundlag af ny eller supplerende videnskabelig viden har begrundet formodning om, at en GMO, der udgør eller indgår i produkter, og som er blevet behørigt anmeldt, og hvortil der er givet skriftlig tilladelse i henhold til dette direktiv, udgør en risiko for menneskers sundhed eller miljøet, kan denne medlemsstat midlertidigt begrænse eller forbyde brug og/eller salg af den pågældende GMO som eller i produkter på sit område...

## 7 EFSAs (2004) opdeling i grupper angiver anvendelsen:

**Group I** EFSAs positivliste over ARM der må bruges uden begrænsning I GMO.
**Group II** må kun bruges på GMO forsøgsmark. Ikke i GMO der sættes på markedet.
**Group III** må hverken anvendes på forsøgsmark eller markedsføres.

## 8 EFSAs (2004) definitioner for klassificeringen

**Group I** contains antibiotic resistance genes which (a) are already widely distributed among soil and enteric bacteria and (b) confer resistance to antibiotics which have no or only minor therapeutic relevance in human medicine and only restricted use in defined areas of veterinary medicine. EFSA (2004) Side 11
**Group II** contains antibiotic resistance genes which (a) are widely distributed in micro-organisms in the environment (soil, plant, water and the mammal gut) and (b) confer resistance to antibiotics which are used for therapy in defined areas of human and veterinary medicine.
**Group III** contains antibiotic resistance genes which confer resistance to antibiotics highly

relevant for human therapy and, irrespective of considerations about the realistic value of the threat, should be avoided in the genome of transgenic plants to ensure the highest standard of preventive health care.

## 9 EFSAs (2004) egne konklusioner:

1. The frequency of horizontal gene transfer from GM plants to other organisms is very low for all three groups of ARMGs considered.

2. For all of the antibiotics and resistances considered, it has been shown or is extremely likely that there is a considerable extant pool of resistance genes already present in the microbiota in the environment.

Altså for alle tre grupper er sandsynligheden for overførsel lille og for alle tre grupper forekommer der allerede resistens i miljøet. Det eneste kriterium der adskiller de tre grupper er altså den behandlingsmæssige værdi.

## 10 EU's lægemidelstyrelses (EMEA) vurdering (2007)

Not withstanding the EFSA opinion, aminoglycosides is a class of antibiotics that has become increasingly important in the prevention and treatment of serious invasive bacterial infections in humans. This is because gram-negative bacteria (and tuberculosis bacteria) are becoming resistant to other classes of antibiotics. Consumption data from Sweden for example show a use of about 5.7 DDD (Defined daily doses) per 1000 inhabitants, or 0.02 DDD/1000 inhabitants and day in 2006, which indicates a 25% increased usage from 2002. In France the consumption is about 0.13-0.15 DDD/Day/1000 inhabitants and relatively stable since 2002[1]. Similar figures come from Estonia (personal communication).

...

The Committees therefore concluded that neomycin, and kanamycin, are of importance for veterinary and human use and that their current and potential future use cannot be classified as of no or only minor therapeutic relevance.

ARM genet nptII kan absolut ikke tilhøre EFSAs Group I.

## 11 EFSA erkender (2007) behandlingsmæssig vigtighed

The GMO Panel agrees with the EMEA that the preservation of the therapeutic potential of the aminoglycoside group of antibiotics is important. EFSA (2007), side 4

## 12 Catch 22

EFSA erkendelses af den vigtige behandlingsmæssige værdi får ikke konsekvens i at omklassificering til group III. EFSA henviser til:

- Lav sandsynlighed for overførsel fra plante til bakterie
- Der eksisterer allerede resistens i miljøet
- Og at nptII genet kun er en ud af flere måde bakterier kan udvikles resistens overfor medicinen.

EFSA lægger jo netop til grund i definitionerne (2004) at disse forhold er gældende for ALLE tre grupper.

**EFSA følger ikke egen logik fordi EFSA fra start valgte at bøje lovgivningen**

## 13 EFSA (2004) indførte af egen drift et hensyn til industri

> TERMS OF REFERENCE
> Recognising the importance and urgency of the question, the GMO Panel has decided to task itself to deliver a scientific opinion on:
> antibiotic resistance genes with the potential to be used as marker genes for genetically modified plants and which may or may not have adverse effects on human health and the environment taking into account the limited availability of alternatives.

Altså, EFSA slækker ulovligt vedtagne miljø og sundhedsbeskyttelse til fordel for kommercielt hensyn. 10-15 år siden ARM var teknisk nødvendigt.

## 14 DK lov ikke vidtgående nok.

Det danske ARM-forbud dækker kun GMO, der indeholder gener, som giver resistens over for antibiotika, der pt anvendes i human- eller veterinærmedicinsk behandling. Som EMEA påpeger (side 2) er der også fremtidige hensyn at tage:

**- ARM-genet kan give resistens også til nye antibiotika der udvikles i fremtiden:**

> ... new chemical entities similar to kanamycin and neomycin could be developed. New chemical entities similar to kanamycin and neomycin could have other properties in relation to, for example, absorption from the gastrointestinal tract and with regard to side-effects. They thus have the potential to become extremely important to treat otherwise multi-resistant gram-negative infections and Tuberculosis.

**- Selv hvor kanamycin ikke anvendes indgår de i epidemiberedskabet for multiresistent tuberculose**

> Aminoglycosides such as kanamycin are currently recommended for treatment in multidrug resistant tuberculosis (MDR-TB). Drug resistance in TB is part of the explanation for the resurgence of TB. WHO estimates that eight million people get TB every year. In the absence of an effective therapy, infectious MDR-TB patients will continue to spread the disease, producing new infections with MDR-TB strains. Until we introduce a new drug with demonstrated activity against MDR strains, this aspect of the TB epidemic could begin to explode at an exponential level (from the Global Alliance for TB Drug development (http://www.tballiance.org).

**- og I beredskabet i tilfælde af "bioterrorism"**

> The EMEA included kanamycin for potential use in MDR-TB in the case of bioterrorism

**- Global eller national forståelse af bekendtgørelsens ordlyd "anvendes"?**
Bør være global pga international karakter af både handel og sygdom

## 15 Løsningen

DK respons bør i første omgang være brug af beskyttelsesklausulen, men på længere sigt bedst at bruge den model EFSA skitserer, men EFSAs egne definitioner skal overholdes.
- To grupper er nok (giver ikke mening at udvikle/forsøgsdyrke noget der alligevel ikke må markedsføres)
- Selve indplaceringen bør overlades til lægefaglige eksperter (EMEA/WHO)

Links til dokumenter:
EFSA (2004) http://www.efsa.europa.eu/EFSA/Scientific_Opinion/opinion_gmo_05_en1,2.pdf
EMEA (2007) http://www.emea.europa.eu/pdfs/human/opiniongen/5693707en.pdf
EFSA (2007) http://www.efsa.europa.eu/EFSA/Statement/gmo_statement_nptII_,0.pdf