

**IN THE MATTER OF  
A PROPOSED COMMISSION DECISION  
CONCERNING THE PLACING ON THE MARKET,  
IN ACCORDANCE WITH DIRECTIVE 2001/18,  
OF A GENETICALLY MODIFIED POTATO PRODUCT**

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**OPINION**

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**INTRODUCTION**

1. I have been asked to advise on the lawfulness of a proposed Commission decision, to be adopted under Article 18(1) of Directive 2001/18 (“the Proposed Decision”). In short, the Proposed Decision would authorise the placing on the market of a genetically modified potato product (derived from *Solanum tuberosum* L. line EH92-527-1) (“the GMO”) containing the antibiotic resistance marker gene (“ARMG”) nptII.
2. For the reasons set out below, the authorisation of the GMO would be contrary to Directive 2001/18 and the Proposed Decision, if adopted, would therefore be unlawful.

## BACKGROUND

3. Article 4(2) of Directive 2001/18 envisages the phasing out of ARMGs in GMOs “which may have adverse effects on human health and the environment”. In the case of GMOs placed on the market in accordance with Part C of the Directive, such ARMGs were to be phased out by 31 December 2004.
4. In theory, there are two ways in which Article 4(2) could be read: (i) as providing for the phasing out of ARMGs that, considered by reference to their intrinsic properties or characteristics, “may have adverse effects on human health and the environment”; or (ii) as providing for the phasing out of such ARMGs only if and to the extent that, because of particular circumstances or the particular use made of them, they “may have adverse effects on human health and the environment”. Under the second interpretation of Article 4(2), an ARMG that, because of its intrinsic properties or characteristics does actually have an adverse effect on human health and the environment would not be phased out if its placing on the market were, for example, subject to conditions that were thought to reduce or eliminate that effect.
5. I do not consider that the second possible interpretation of Article 4(2) is correct. Both the wording of Article 4(2) and the legislative history indicate that the intention was to phase out ARMGs that, by reference to their intrinsic properties or characteristics, “may have adverse effects on human health and the environment” irrespective of their intended use or the conditions that might be placed upon any authorisation granted. For example, in the Opinion of the Commission on the European Parliament’s amendments to the Council’s Common Position (COM(2000) 293 final, under Amendment 48), the Commission stated unambiguously: “The Commission is of the opinion that antibiotic resistance market genes need to be phased out and be replaced with alternatives as soon as practically possible. A phasing out is foreseen in the Common Position”. Further, “phasing out” would be inappropriate if the

concern arose only in relation to ARMGs that posed a threat because of a particular use to be made of them or if no relevant conditions were included in an authorisation: if either situation were the problem, the solution would be to refuse authorisation for the use in question or impose appropriate conditions, not phase out the ARMG.

6. Accordingly, an ARMG that is intrinsically capable of adversely affecting human health and the environment cannot be excluded from the class of ARMGs to be phased out under Article 4(2) merely because, in a particular case, it might be thought that steps could be taken to prevent that ARMG from actually having that effect.
7. That conclusion is consistent with the precautionary principle (which is to be applied to the interpretation and application of the Directive: *cf.* recital (8) of the preamble).
8. In determining whether or not, by reason of its intrinsic properties or characteristics, an ARMG “may have adverse effects on human health and the environment”, it is necessary to exercise a judgment based upon up-to-date scientific information and it is also necessary to bear in mind the precautionary principle (see recital (8) of the preamble to the Directive).
9. In an Opinion adopted on 2 April 2004 concerning the use of ARMGs as marker genes in genetically modified plants (“the 2004 Opinion”), EFSA classified ARMGs into three groups on the basis of two criteria: (i) the presence of ARMGs in soil, plant, water and enteric bacteria; and (ii) the importance of specific antibiotics in therapeutic use (see paragraph 6 of the 2004 Opinion).
10. When considering EFSA’s classification, it must be borne in mind that EFSA had concluded that: (i) the frequency of horizontal gene transfer from GM plants to other organisms is “very low for all ARMGs considered” (see the

third paragraph of the “Summary” section of the 2004 Opinion and point 1 on page 13); and (ii) each of the groups identified by EFSA includes ARMGs that are, or are likely to be, widespread in the environment (see point 2 on page 13 and, in relation to Group III, paragraph 5.7 of the 2004 Opinion).

11. Accordingly, the material difference between the ARMGs falling into the different Groups lies in the therapeutic importance of the antibiotics to which they confer resistance, which rises from “no or only minor therapeutic importance and restricted use” in Group I to “highly relevant” in Group III.
12. The nptII gene was placed by EFSA in Group I, which contains ARMGs that: (i) are already widely distributed among soil and enteric bacteria; and (ii) confer resistance to antibiotics having no or only minor therapeutic relevance and restricted use (see paragraph 6.1 of the 2004 Opinion). That classification was based in part on EFSA’s view that nptII affected the following antibiotics: kanamycin, neomycin and geneticin (see page 7 of the 2004 Opinion).
13. Group II covers ARMGs that are: (i) widely distributed in micro-organisms in the environment; and (ii) “confer resistance to antibiotics which are used for therapy in defined areas of human and veterinary medicine” (see paragraph 6.2 of the 2004 Opinion). EFSA considered that ARMGs in Group II should be used only for field trial purposes and should not be present in GM plants to be placed on the market (see the penultimate paragraph of the 2004 Opinion).
14. Group III covers ARMGs that “confer resistance to antibiotics highly relevant for human therapy”. Having regard to the importance of such antibiotics in clinical usage, EFSA took the view that ARMGs falling within Group III should be avoided in the genome of transgenic plants “irrespective of considerations about the realistic value of the threat” (paragraph 6.3 of the 2004 Opinion) and recommended that they should not be “present in GM plants to be placed on the market or in plants used for experimental field trials” (see the last paragraph of the 2004 Opinion).

15. So far as Group III is concerned, it is clear from the 2004 Opinion that EFSA took the view that, even though the frequency of horizontal gene transfer was very low and even though there was (or was likely to be) widespread naturally occurring resistance to the antibiotics in question, the importance of the antibiotics in question outweighed those other considerations and justified its recommendation.
16. That exercise of judgment seems to have been an application of the precautionary principle and is certainly consistent with that principle. On the other hand, it is not entirely clear that EFSA's approach was wholly consistent with Article 4(2) of Directive 2001/18.
17. Based on the wording of Article 4(2), it is arguable that the only relevant consideration is whether or not the ARMG "may have adverse effects on human health and the environment". Focusing for the moment solely on adverse effects on human health, that test may be satisfied if the ARMG expresses resistance to antibiotics used in human medicine. On one view, it is not necessary to consider anything else.
18. EFSA seems to have taken the view that, in order to answer the question whether or not an ARMG may have adverse effects, it is not sufficient to look at the intrinsic properties or characteristics of the ARMG; it is also necessary to consider the chances that the presence of the ARMG in a GMO will have adverse effects on human health and the environment.
19. EFSA does not seem to have been able to exclude the possibility of any of the ARMGs that it was considering having *some* adverse effect on human health and the environment. Its approach seems to have been based upon the idea that the degree of risk should be balanced against the anticipated consequences if the risk eventuated.

## **THE SCIENTIFIC BASIS FOR AUTHORISATION OF THE GMO HAVING REGARD TO ITS ARMG CONTENT**

20. In an Opinion adopted on 7 December 2005 (which appears to be the Opinion referred to in recital (8) of the preamble to the Proposed Decision, which states that it was published on 24 February 2006 – for that reason referred to here as “the 2006 Opinion”), EFSA stated that the GMO was “unlikely to have an adverse effect on human health or the environment in the context of its proposed uses”: see the last paragraph of the “Summary” section.
21. EFSA evaluated the GMO from a number of different perspectives. So far as is here relevant – that is, so far as the significance of the nptII gene as an ARMG contained in the GMO is concerned – EFSA relied upon its 2004 Opinion, which had described kanamycin, neomycin and geneticin as of no or only minor relevance for therapeutic purposes: see, for example, paragraphs 4.2.3.2 and 5.2.2(a) of the 2006 Opinion. EFSA’s view was, as noted above, based upon its balancing of the level of risk against the anticipated consequences if the risk eventuated.
22. In February 2007, EMEA issued an opinion on the importance of the antibiotics affected by nptII (“the EMEA Opinion”) in response to a request from the Commission that was, in turn, prompted by a WHO report that classified gentamicin, kanamycin and neomycin (amongst others) as “critically important antibacterials”.
23. EMEA stated that kanamycin and neomycin “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”: first paragraph under the heading “Overall conclusions from Human and Veterinary [Committees]”.
24. It should also be noted that: (i) in the first paragraph of the EMEA Opinion, it is stated that nptII codes for an enzyme that generally confers resistance to

several antibiotics other than the ones referred to by EFSA in its 2004 Opinion, including gentamicin B; (ii) EMEA regarded the importance of gentamicin as “undisputed” and the omission of gentamicin from EFSA’s evaluation as “crucial” (see point 2 of the annex to the EMEA Opinion); (iii) EMEA based its views upon “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)” (*ibid.*) and therefore restricted itself to a consideration of those antibiotics; and (iv) EMEA considered that “occurrence of resistance to neomycin and kanamycin varies substantially between countries and bacterial species” (see point 5 of the annex to the EMEA Opinion).

25. It appears that the Commission then requested EFSA “to consider the information provided by the EMEA and to indicate the possible consequences of the EMEA’s conclusions on the safety assessment of the nptII gene...” (see the last paragraph of the “Background” section of EFSA’s subsequent Statement adopted on 22-23 March 2007 – “the 2007 Statement”).
26. On the assumption that the Commission framed its request to EFSA in the way indicated in the passage quoted above from the 2007 Statement, EFSA had to address at least three significant comments made by EMEA: (i) the importance of the antibiotics affected by the nptII gene; (ii) the concern expressed about the possible effect on gentamicin; and (iii) the variability of natural resistance to neomycin and kanamycin.
27. EFSA’s response is contained in the 2007 Statement.
28. In the first paragraph of the section entitled “Conclusions”, EFSA stated: “The GMO Panel agrees with the EMEA that the preservation of the therapeutic potential of the aminoglycoside group of antibiotics is important” (that is the group that includes gentamicin, kanamycin and neomycin).

29. On the basis of the classification adopted by EFSA in the 2004 Opinion, that would therefore move nptII into Group III, leading to the conclusion that the GMO could not be authorised because of the presence of nptII.
30. At the very least, it would have led to the classification of nptII in Group II, leading to the restriction of the use of the GMO to field trials.
31. However, in the 2007 Statement, EFSA did not draw those conclusions, although it never disavowed the 2004 Opinion or the reliance placed upon it in the 2006 Opinion.
32. The 2007 Statement does not address expressly the concern expressed by EMEA about gentamicin. Accordingly, it is not clear if EMEA's assumption (that the substrate specificity of the product of the nptII gene used as marker in the GMO is really restricted to neomycin, kanamycin and geneticin) is correct. If gentamicin is affected, that would reinforce the classification of nptII in Group III; but, if gentamicin is not affected, that may not matter given EFSA's acceptance of the importance of the aminoglycoside group of antibiotics.
33. The 2007 Statement also does not address EMEA's concern about the variability of natural resistance. EFSA does not state that EMEA's concern is ill-founded. It simply does not mention it. There is no indication that EFSA has even addressed its mind to EMEA's concern, let alone tried to evaluate it.
34. The 2007 Statement is therefore inconsistent with the approach followed by EFSA in the 2004 and 2006 Opinions and does not address concerns raised by EMEA that, on the face of it, call for consideration.
35. So far as can be seen, the 2007 Statement is based upon two factors (or "key elements"): (i) the low likelihood of gene transfer; and (ii) the prevalence of

the nptII gene (see the section of the 2007 Statement headed “Assessment” and the first paragraph of the section headed “Conclusions”).

36. The second factor (or “key element”) appears on the face of it to be undermined by the point raised by EMEA (which EFSA has not rejected or, apparently, considered or evaluated), namely, the variability of the natural occurrence of resistance. If natural resistance is variable, the impact of nptII would also be variable (in relative terms).
37. However, more fundamentally, the 2007 Statement is impossible to reconcile with the 2004 Opinion.

## **CONCLUSION**

38. The result is that, in my view, the Commission does not have a proper scientific basis on which to conclude that the GMO can lawfully be authorised.
39. Following the approach used by EFSA, and bearing in mind the further information provided by EMEA that has not been disputed by EFSA, the position is that there are a low likelihood of gene transfer and variable degrees of prevalence of natural resistance (which means that the importance of natural resistance will be less in some place than in others); but those factors have to be weighed against the fact that nptII confers resistance on an important group of antibiotics (and therefore “may have adverse effects on human health and the environment”).
40. EFSA’s considered view in 2004 was that, in such circumstances (I use the word “such” although, in 2004, EFSA may not have taken into account the implications of the variability of natural resistance), a GMO containing such an ARMG should not be authorised for placing on the market. The 2007

Statement does not set out any new fact or new information that would justify a different conclusion.

41. In order to circumvent the obstacle to the authorisation of the GMO presented by the 2004 Opinion, it would be necessary for the Commission to adopt a different methodology from that used by EFSA in that Opinion. However, in my view, any alternative methodology is problematical because, on the basis of the scientific information currently available: (i) nptII confers resistance to antibiotics that are of “critical importance” (to use WHO’s phrase); and (ii) the risk of gene transfer and a further increase in resistance to those antibiotics (which, due to variations in natural resistance, may be greater in some areas and lesser in others) has not been excluded.
  
42. Further and in any event, if the correct interpretation of Article 4(2) of Directive 2001/18 is that an ARMG is to be phased out if, by reason of its intrinsic properties or characteristics, it may adversely affect human health and the environment, the undisputed fact that nptII confers resistance to antibiotics used in human medicine is sufficient to render the authorisation of the GMO unlawful: it is very difficult to see how a GMO could be authorised in 2008 if it contained an ARMG that should have been phased out by 31 December 2004.

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