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European Communities – Measures Affecting the Approval and Marketing of Biotech Products

(DS291, DS292, DS293)

Third Party Submission by Norway

Geneva 24 May 2004

1. INTRODUCTION

1.1 Overview of the cases

1. The present case addresses certain issues relating to the trade and marketing of Genetically Modified Organisms (hereinafter referred to as "GMOs") and products that incorporates such GMOs (hereinafter referred to as "GM products"). More specifically, the United States (USA), Canada and Argentina (hereinafter referred to collectively as "the Complainants") have challenged the European Communities' (EC) so called "moratorium" relating to approval of GMOs, both an alleged "General Moratorium" on the assessment and approval of new applications and a "Product-Specific Moratoria" relating to applications where the process of assessment and approval had started, but allegedly has been stopped. In addition the Complainants claim that national EC Member States' measures on certain GMOs authorised by the EC violate WTO obligations.[1]

2. The Complainants claim that the challenged EC and EC Member States measures violate a number of provisions of the Agreement on the Application of Sanitary and Phytosanitary Measures (the SPS Agreement); the Agreement on Technical Barriers to Trade (the TBT Agreement); and the General Agreement on Tariffs and Trade 1994 (the GATT 1994, also subsequently referred to as "the GATT"), as described in their panel requests and as further elaborated in their written submissions.

3. The Government of Norway (hereinafter referred to as "Norway") has, as will be demonstrated below, substantial trade as well as systemic interest in the matter before the Panel, and has therefore requested third party status.

4. Norway in general supports the views presented by the EC in its first written submission, the essence of which is that GMOs are new and GM products are complex products, and that a prudent approach is therefore required in the assessment of possible risks posed by

[1] The first written submissions of the US, Canada and Argentina, respectively.

GMOs and GM products. Decisions on the marketing of GMOs and GM products should be based on a sound and comprehensive legal framework.

5. Norway would underline that we recognise the many potential benefits from GM products.

6. However, Norway cannot subscribe to the unreserved description of the sole benefits of GMOs given by the US in their submission.[2] In our view it is important to keep in mind that the technologies which produce GMOs are new and that important effects on health and the environment remain not fully understood. Thus, Norway agrees with the EC that the approval of GMOs and GM products raise several complex issues of scientific and factual nature. The process of assessment of the risks is complex and therefore also legitimately time-consuming. Based on today's scientific knowledge, a prudent approach in WTO members' regulatory frameworks is therefore warranted.

7. In Norway's opnion it is necessary to address the particularities of each and every GMO when it comes to risk assessment. GM products are relatively new developed during the past 20 years.[3] The risks related thereto, and any associated consequences to health and the environment, are therefore in many respects not yet fully assessed. It is, furthermore, of utmost importance to understand that possible risks associated with a GMO are particular to that genetic modification and particular to the particular environment where it is introduced. When evaluating the risks posed by GMOs "no one size fits all".

8. While the SPS Agreement was not drafted with the explicit intention to deal with the particular challenges that GMOs pose to international trade, newer international legal instruments and standards have recognised the particular risks inherent in the use of certain GMOs. These legal frameworks attempt to strike the necessary balance between an open and non-discriminatory multilateral trading system on the one hand, and the necessary means in order to avoid adverse effects of GMOs on the other. When

[2] Described in paragraphs 17 – 29 of US first written submission.
[3] See EC first written submission footnote 13.

interpreting and applying the relevant WTO agreements (SPS, TBT or GATT), the Panel should therefore take account of such international legal instruments and standards[4].

1.2 The focus of the Norwegian Submission. Summary of arguments.

9. Norway will not address all the legal issues raised in this case, but restrict this third party submission to certain issues of particular importance to Norway. Norway does, however, reserve the right to address other issues in its oral intervention before the Panel.

10. Norway will address the risks associated with three particular GMOs: Bt. 176[5], MS1xRF1[6] and Topas 19/2[7]. These are three out of seven GMOs in relation to which national EC Member State measures are contested in the present case.

11. Norway's focus on these three GMOs is due to the fact that they contain *antibiotic resistence marker genes (ARMG),* and this is the main reason why marketing of them is prohibited in Norway.

12. Norway intends to show, by way of a presentation of our own risk assessment on these products, that EC Member State national measures relating to those GMOs were justified under the WTO Agreement. The reason being that at the time relevant scientific evidence allowed such measures to be taken because the existence of an unacceptable level of adverse effects on health and/or environment could not be excluded on the basis of available pertinent information.

13. Norway will argue that the risks associated with *ARMGs* do not fall within the SPS Agreement, as such risks do not fall within the definition of Annex A, paragraph 1 of the SPS Agreement. Not to allow GMOs with ARMGs does not fall within the TBT Agreement, but is regulated by GATT 1994. The legal issues will be elaborated in Chapter 3 of our submission.

[4] I.e: work by the the Codex Alimentarius Commission, and also the Cartagena Protocol on Biosafety of 29 January 2000 (herinafter referred to as "Cartagena Protocol" or "Biosafety Protocol") to the United Nations Convention on Biodiversity. The Cartagena Protocol entered into force on 11 September 2003.
[5] Subject to safeguard in Austria, Luxembourg and Germany.
[6] Subject to safeguard in France.
[7] Subject to safeguard in France and Greece.

2. FACTUAL BACKGROUND

14. In order to address the questions at issue in this case, it is important to understand the genetic modifications at issue for the GMOs for which measures have been taken, and the particularities of *Antibiotic Resistance Marker Genes (ARMG)*. In the present chapter we detail the techniques used, the possible adverse effects, the regulatory approaches and the risks associated in particular with the three GMOs that Norway is addressing in this submission.

2.1 Definition of GMO and description of techniques for genetic modification and the potential benefits of GMO

15. GMOs are one of the results of modern biotechnology and are created by a particular set of techniques which are used to genetically modify (or "genetically engineer") organisms. In short, it is a change of genetic material within an organism through genetic recombinant nucleic acid techniques.[8]

16. The EC has provided a fully satisfactory definition and description of techniques for genetic modification and the potential benefits of GMO in their first written submission[9], which we incorporate by reference into this submission.

17. Additionally to the arguments presented by the EC, it does, however, seem necessary to point out that USA, in their first written submission, uses the phrase "*modern biotechnology*" to refer to "*recombinant DNA*" technology. As pointed out in FAOs[10] press release concerning FAO's annual report "*The State of Food and Agriculture 2003-04*"[11]; "[b]*iotechnology, one of the tools of the gene revolution, is much more than*

[8] See definition in Article 3(g) and (i) of the Cartagena Protocol on Biosafety;
3(g): "Living modified organism" means any living organism that processes a novel combination of genetic material obtained through the use of modern biotechnology;
3(i): "Modern biotechnology" means the application of:
a. nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or
b. fusion of cells beyond the taxonomic family,
that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.
(http://www.biodiv.org/biosafety/articles.asp?1g=0&a=bsp-03)

[9] In respect of the definitions, see *EC – First written submission*, paras. 17-19. In respect of techniques, see *EC – First written submission*, Chapter II.A.2. In respect of benefits, see *EC – First written submission*, Chapter II A.3.

[10] Food and Agriculture Organization of the United Nations (FAO).

[11] See FAO Press Release "The gene revolution: Great potential for the poor, but no panacea", 17 May 2004 (http://www.fao.org/newsroom/en/news/2004/41714/index.html (Exhibit NOR-1)

genetically modified organisms (GMOs), sometimes also called transgenic organisms", which are at issue in this case. Consequently, some of the potential benefits described in the paragraphs 17-26 of the first written submission of USA might not derive from GMOs, but other forms of modern biotechnology.

18. Regarding the potential benefits it should also be mentioned, as stated in the FAOs press release concerning FAO's annual report *"The State of Food and Agriculture 2003-2004":*[12] *"[b]iotechnology holds great promise for agriculture in developing countries, but so far only farmers in a few developing countries are reaping these benefits* [-.] *Basic food crops of the poor such as cassava, potato, rice and wheat receive little attention by scientists* [-.] *Neither the private nor the public sector has invested significantly in new genetic technologies for the so-called 'orphan crops' such as cowpea, millet, sorghum and tef that are critical for the food supply and livelihoods of the world's poorest people.*"

19. Furthermore, while not refuting that benefits exist, the picture drawn by the USA with respect to the safety record of recombinant DNA technology[13] gives an incomplete - if not misleading - description of the consequences of GMOs. Norway does not support the view that there is a "proven safety record" of recombinant DNA technology".

20. As pointed out by the FAO in the press release mentioned above, the potential benefits and risks of GMOs need to be carefully assessed case by case, that the legitimate concerns for the safety of each transgenic product must be addressed prior to its release and that careful monitoring of the post-release effects of these products is essential. It is furthermore stated that the scientific evidence concerning the environmental and health impacts of genetic engineering is still emerging, that little is known about long-term effects of foods derived from transgenic crops and that there is less scientific agreement on the environmental impacts of transgenic crops.

21. The United States seems oblivious to the need to undertake assessments of potential risks from GMOs. Indeed, possible adverse effects of GMOs are not mentioned at all by the United States in their first written submission, which focuses on alleged benefits. However, as clearly pointed out by the FAO, the potential risks associated by GMOs must

[12] See FAO Press Release "The gene revolution: Great potential for the poor, but no panacea", 17 May 2004 (http://www.fao.org/newsroom/en/news/2004/41714/index.html (Exhibit NOR-1)

[13] US First written Submission, paragraphs 27 and 28.

be assessed, and on a case by case as genetic modifications may have different implications in different species and environments. In this Chapter Norway will therefore seek to give a more balanced picture of the consequences of GMOs and the specific challenges related to risk assessments of GMOs, as well as the risks associated with the three particular GMOs that we are addressing in this submission.

2.2 Possible adverse effects of GMOs. An overview.

2.2.1 Introduction

22. As has been documented by the EU in paragraphs 67-131 of its First Written Submission, and elaborated in Chapter 2.3 below, Governments, authorities and international organisations have developed regulatory approaches specific to GMOs, hereunder regulations and guidelines for risk assessments of GMOs, due to worries related to safety of GMOs.

23. From the 1970s up until today, there has been an increased focus on possible risks to the environment and human health connected to the development, environmental release and the use of GMOs as food and feed. In the same period there has also been an increase in the research activity focusing on potential adverse effects from GMOs.

24. In Norway's opinion this clearly demonstrates that – contrary to what is claimed by the United States in *paragraph 11* of its first written submission - GMOs are not simply a continuation of traditional breeding and completely safe. They are not – and should not be treated as – equivalent to non-GM products.

25. One important reason for this is that this technology involves possibilities that cannot be achieved by traditional breeding. Novel genotypes created through gene technology cannot draw on the tradition for safe use as applied to new cultivars of traditionally bred crops.

26. There are in general extensive unpredictability's related to i) to the expression of the foreign genes inserted into the organisms, and ii) the possible side effects coming from the position of the inserted genes within the genome of the recipient organism and iii)

possible long-term evolutionary consequences of introducing novel DNA into evolving populations.

27. The position of the foreign genes, when inserted through gene technology is random within the chromosomes of the engineered plants. Small fragments of DNA often ends up in places in the chromosomes giving unpredictable effects. In addition, secondary effects of introduction of the transgene(s) may arise from the expressed products of the new genetic material, or the insertion(s) may cause pleiotropic effects, which divert the gene expression patterns of the recipient organisms. Changes of/in the GMO or its product may have unexpected effects on protein production and in metabolic activities. In other words the gene technology is not as precise as many – including the USA in paragraph 11 of their First Written Submission - have argued.

28. Another important reason is – as stated by the FAO in the press release mentioned in Chapter 2.1 above - that the scientific evidence concerning the environmental and health impacts of genetic engineering is still emerging, that little is known about long-term effects of foods derived from transgenic crops and that there is less scientific agreement on the environmental impacts of transgenic crops.

29. Finally, it is important to be aware of the fact that especially environmental studies are usually difficult to conduct due to lack of appropriate methodologies, basic knowledge and baseline data of the effect in focus. It is also hampered by lack of access to research material (e.g. transgenic plant material and their unmodified counterparts), as companies developing GMOs may be reluctant to distribute their material to independent 3rd parties for research purposes. The restricted access to the exact genetic modifications done and the risk assessment done by companies, should also be mentioned in this context.

30. In the Section below we will briefly describe the main potential environmental effects outlined by scientists and the main scientific concerns raised in connection with human and animal health.

2.2.2 Effects of genetically modified plants ("GMP") - findings referred to in scientific literature

2.2.2.1 Environmental effects

2.2.2.1.1 Introduction

31. The following have been outlined by scientists as possible effects[14]:

- The spreading of genes through hybridisation between GMPs and closely related domesticated or wild species.
- Population growth, spreading and invasion of GMPs into natural ecosystems.
- Increased competition from GMPs or their hybrids with natural species.
- The spreading of genes through horizontal gene transfer from plants to microorganisms in the environment.
- Development of herbicide resistant weeds.
- Development of insects resistant to insecticides.
- Effects on non-target organisms.
- Secondary environmental effects as a consequence of changed agriculture practises e.g. new use of insecticides, herbicides, fertiliser's etc.

32. Some of the hypothesises in the bullet points above have been debated in the scientific literature and many of them have been verified by research in some species and environments as will be shown below.

[14] Keeler K.H. 1985 (Exhibit NOR-77); Crawley, M.J., 1988. Meeting report: COGENE/SCOPE at Lake Como. Special combined issue: Trends Biotechnology & Trends Ecology, Evol 3. 2-3 (Exhibit NOR-78); Ellestrand N.C. 1988. Special combined issue: Trends Biotechnology & Trends Ecology, Evol 3. 30-32 (Exhibit NOR-79); Tidje J.M (and 6 others) 1989. Ecology. Vol 70, No 2 (Exhibit NOR-80); Williamson M. 1989. Special combined issue: Trends Biotechnology & Trends Ecology, Evol 3. 32-35 (Exhibit NOR-81); McNally R. 1994. The Ecologist, Vol 24, No. 6 Nov/Dec, 207-212 (Exhibiy NOR-82); Doyle J.D, Stotzky G, McClung G, Hendricks C.1995. Advances in Applied Microbiology, Vol. 40, 237-287 (Exhibit NOR-83); The Royal Society of Canada. 2001. Elements of Precaution: Recommendations for the regulation of food biotechnology in Canada. An expert panel report on the future of food biotechnology prepared by the Royal Society of Canada at the request of Health Canada, Canadian Food Inspection Agency and Environment Canada (ISBN 0-920064-71-x) (Exhibit NOR-22); Snow A.A. *et al.*, 2004; "Genetically engineered organisms and the environment: Current status and recommendations" ESA position paper (Exhibit NOR-4)

33. A consequence of the points above may be population decrease or extinction of species in natural ecosystems, or different type of problems for agriculture. Whether these types of effects will occur is difficult to predict a priori, and will depend on the species and genetic modification in question, the receiving environment or the farming and agro-ecosystem in use.

2.2.2.1.2 The spreading of genes through hybridisation between GMPs and closely related domesticated or wild species

34. The spreading of genes through hybridisation could lead to loss in biodiversity. In addition it could lead to problems related to the co-existence between farming based on GMPs on one hand and conventional and organic farming on the other hand, and development of herbicide-resistant weeds as will be pointed out in Chapter 2.2.2.1.3.

35. Some experiments carried out in late 1980s by Monsanto and published in 1990[15], showed that oilseed rape or canola (*Brassica napus*) could hybridise with the wild mustard (*S. arvensis*), one important weed in USA, but the hybrids did not produce hybrid seeds. The same study showed that crossing with some other wild species could occur but only at very low frequencies.

36. In these studies it could not be demonstrated out-crossing on distances above 100 metres. On this basis Monsanto proposed a buffer zone of 300 meters for experimental releases with this species to the authorities of Canada. In 1989 they found three cases of hybridisation on a distance of 225 metres.

37. The understanding of possible environmental and agricultural risks from oilseed rape has changed much since these experiments. In newer research it has been demonstrated cases of out-crossing by rapeseed on distances up to 3 km[16], and that the out-crossing rates are dependent on the oilseed rape variety, the size of the fields, and factors influencing pollination by wind and insects. It is also found that hybridisation with wild relatives and hybridisation with many different wield relatives, e.g. field mustard *B. rapa;* black

[15] Muench S.R. 1990 (Exhibit NOR-84)
[16] Rieger M.A, Lamond M. Preston C., Powles S.B., and Roush T.R . 2002. Science, Vol 296 28 June, 2386-2388 (www.sciencemag.org) (Exhibit NOR-85)

mustard *B. nigra* and wild *B. Camprestis*[17], and that the hybrids are producing viable hybrid seeds.

38. Another important case that has been criticised and thoroughly debated during the last three years, was the reported unintentional spread and hybridisation of genetically modified maize in Mexico[18]. This case has been described by the EU in paragraph 63 of its First Written Submission.

2.2.2.1.3 Development of herbicide resistant weeds

39. Development of herbicide resistant weeds may lead to future agricultural problems connected to weed management, and may also pose a risk to European agriculture and environment. It may be necessary to increase the use of herbicides and to use different herbicides that are more harmful to human health and the environment, in order to kill the weeds. This is quite the opposite of what is claimed to be one of the potential benefits of GMOs.

40. Today many genetically modified varieties of oilseed rape is produced commercially in North America, and it is also found herbicide resistant conventional oilseed rape due to out-crossing from herbicide resistant genetically modified oilseed rape. It is in Canada found unintended multi resistant hybrids of different genetically modified oilseed rape varieties against the herbicides glyfosat, glufosinat ammonium and imidazolin[19].

[17] Mikkelsen *et.al.* 1996 (Exhibit EC-34); Jørgensen R.B. 1999 BCPC Symposium Proceedings No 72 Gene flow and agricultue: Relevance for transgenic Crops(Exhibit NOR-86);Landbo L. and R. B. Jørgensen, 1997. Euphytica 97, 209-216 (Exhibit NOR-87); Stewart C. N., All J. N. Raymer P. L., and Ramachandran S. 1997. Molecular Ecology 6, pp773-779 (Exhibit NOR-88); Kvaløy K. 2001. Environmental risks releated to the release of genetically modified plants with the focus on oilseed rape (*Brassica napus*), Norwegian Institute for Nature Research, NINA Project Report 15 (Exhibit NOR-5)

[18] Quist D. and Capela I.H. 2001. Nature Vol. 296 (Exhibit NOR-89)

[19] Hall *et al*.Good "Pollen flow between herbicide-resistant Brassica napus is the cause of multipleresistant B. napus volunteers", 48 Weed Science 688, 2000(Exhibit EC-37); The Royal Society of Canada. 2001. Elements of Precaution: Recommendations for the regulation of food biotechnology in Canada. An expert panel report on the future of food biotechnology prepared by the Royal Society of Canada at the request of Health Canada, Canadian Food Inspection Agency and Environment Canada (ISBN 0-920064-71-x) (Exhibit NOR-22)

41. It has also been reported contaminated varieties of oilseed rape in Canada, USA and EU with genetically modified varieties that are not approved by the authorities[20]. Such contamination may take place both through out-crossing from experimental fields or via mixing during the transportation chain. If such contamination comes from varieties that are part of experimental field releases, they have not been through risk assessments, and may therefore pose completely unknown risks both for the environment and human health.

2.2.2.1.4 Effects on non-target organisms

42. Plants which have been genetically modified to produce substances that are toxic to some target organisms which harm the agricultural crops, for example the GM Maize line Bt176, could also harm non-target organisms and consequently cause harm to biological diversity.

43. It has been demonstrated in laboratory experiments that Bt-producing pollen from genetically modified maize (corn) can kill monarch butterfly larvae, a non-target insect[21]. This experiment has been criticised by some scientists due to the use of too high concentrations of Bt-pollen on the leaves the larvae eat, and that it was laboratory experiments that did not reflect natural conditions. In this regard it should be mentioned that most of the toxicological studies used as bases for risk assessments in applications for commercial release by the biotechnology industry, is based on laboratory studies that do not reflect natural conditions.

44. Another repeated study conducted with the amount of Bt-maize pollen that can be found on leaves from the plant Milkweed close to maize fields, did also show increased mortality of the monarch butterfly larvae[22].

45. Most of the possible non-target insects in Europe that may be associated with commercial field production of genetically modified Bt-maize have never been tested in toxicological studies, and therefore we do not know whether they are susceptible for toxin producing Bt-plants or not. Most of the Lepidoptera insect families include species that are

[20] Mellon M and J. Rissler, 2004. Report from: Union of Concerned Scientists, Gone To Seed – Transgenic Contaminants in the Traditional Seed Supply (Exhibit NOR-6)
[21] Losey J. E, Rayor S. L, Carter M. E. 1999. Nature. Vol 399, 20 May (www.nature.com))Exhibit NOR-90)

vulnerable for some of the different strains of Bt-toxins that are known and in use[23]. But most of the research is conducted with Lepidoptera species that are known plant-pests, and only a small part of the potential vulnerable species is therefore tested.

46. A difference, pointed out by many scientist, when comparing traditional spraying of Bt (*Bacillus thuringiensis*) as an insecticide with the strategy of incorporating the toxin producing gene within plants, is that the toxin will always be available for insects and other organisms in the field. It will not be washed away with the first rain, something that may increase the possible negative effect on non-target insects and also accelerate the possible development of resistant insect towards the Bt-toxin. Usually it will also be left behind much plant material with the Bt-toxin in the field after harvesting. Effects of Bt-plant material on soil biodiversity are little studied, but some studies have demonstrated that Bt-toxin is released into the soil from roots and decaying Bt-plant material[24], and studies indicate that Bt-toxins can accumulate in the soil, implying that soil living organisms can be exposed for the toxin over a long time. It is also found indications that the earthworm (*Lumbricus terrestris*) can be effected when fed Bt-corn litter in experiments. It is therefore proposed that extended pre- and post-commercial monitoring is necessary to assess the long-term impact of Bt-toxin in transgenic plant residues on soil organisms[25].

47. Studies conducted in Switzerland[26] showed a clearly increased mortality involving the non-target predatory insect Lacewings (*Chrysoperla carnea*) in tritrophic studies using Bt-maize plants. This finding was one of the first studies illustrating that non-target predatory insects may have increased mortality when predating on herbivore insects that are feeding on gene modified Bt-plants. Predatory insects as Lacewings are important insects in natural biological control systems and have also significant ecological functions in the agro-ecosystems. This type of studies are important in relation to risk assessments, and should have been conducted with all varieties of genetically modified plants, but

[22] Shelton A. M. and Sears M.K. 2001, The plant Journal 27(6), 483-488 (Exhibit NOR-92)
[23] Drummond and Pinnock, 1994, abstract (Exhibit NOR-93)
[24] Sims and Holden, 1996, abstract (Exhibit NOR-94); Saxena *et al*., 1999, abstract (Exhibit NOR-95);Saxena and Stotzky, 2000, abstract (Exhibit NOR-96);
Zwahlen C. *et al.,* 2003 (Exhibit NOR-97)

[25] Zwahlen C. *et al.,* 2003 (Exhibit NOR-97)
[26] Hilbeck A. and F. Bigler, 1999 (Exhibit NOR-98)

especially with Bt-plants, and should include major insect species associated with the cultivation of the plant species in focus. It is also found in experiments a decline in fecundity and life length of two-spotted ladybird interacting with aphis living on gene modified lectin-producing potatoes[27].

2.2.2.1.5 Secondary environmental effects as a consequence of changed agriculture practises

48. The use of GMPs in agriculture in many cases leads to changes in agricultural practices that could cause harm to biological diversity.

49. In 2003 The Royal Society of United Kingdom reported on the farm scale evaluation of spring-sown genetically modified crops[28]. This was a comprehensive farm scale experiment of possible effects of genetically modified herbicide tolerant (GMHT) crops on farmland biodiversity. The investigation was conducted across Great Britain during 2000-02 in approximately 60 fields of each beet, maize and oilseed rape, with the tolerance against glufosinate-ammonium (maize and rape), and glyphosate (beet). One of the aims of this project was to evaluate whether gene modified herbicide tolerant crops through the changes in agricultural management practises could influence weeds, invertebrates and their food webs.

50. The results from the farm scale study are complex and it is difficult to draw conclusive conclusions on farm management and environmental implications from growing genetically modified herbicide tolerant crops. The results however clearly show the uncertainties regarding possible environmental effects, and that these effects cannot be assessed on a general basis or assumptions. It also demonstrates that many variable factors and interactions have to be considered and that many of those are poorly understood.

[27] Birch A.N.E. *et al.*, 1999 (Exhibit NOR-99)
[28] (Exhibit EC-39 and EC-40)

2.2.2.1.6 The spreading of genes through horizontal gene transfer from plants to microorganisms in the environment.

51. Horizontal gene transfer[29] is a natural phenomenon that has been linked to the possibility of negative effects from genetically modified plants. To day no scientists deny the occurrence of horizontal gene transfer, and different mechanisms has been described for the process[30]. It is reported an increasing amount of genes and traits in different species that most probably have been spread through horizontal gene transfer[31].

52. Horizontal gene transfer means that intentional genetic modification of for example plants could lead to unintentional genetic modification of other organisms. The consequences of these unintentional genetic modifications are not very well known, and are therefore among the uncertainties related to the effects of GMPs on human health and the environment and their possible long-term effects.

53. Horizontal gene transfer of antibiotic resistance marker genes from genetically modified plants to pathogenic microorganisms has been debated in connection to many risk assessments[32]. Antibiotic resistance marker genes are used as a selection tool during the process of modification, and in most cases remain within the plant as an intact genetic trait. Resistance towards antibiotics is an increasing problem in therapeutic human and veterinary medicine. This resistance development in pathogenic bacteria is most probably due to unwise use and spread of antibiotics in general. The two debated uncertainties are:

i) What possible increased spread of antibiotic resistance genes may occur through horizontal gene transfer from GM plants to organisms in the environment and in the human and animal digestical tract when the plants are digested?

[29] One definition of horizontal gene transfer is *"any occurrence of heritable material passing between organisms, asynchronous with reproduction of the organisms. It represents replication of heritable material outside the context of parent to offspring (i.e. vertical) reproduction"*. Heinemann J. A. 2003. New Zealand, Bioscience 12, 51-55 (Exhibit NOR-102)

[30] Syvanen M. 1984 (Exhibit NOR-103); Heinemann J. A. 1991. TIG vol. 7 No 6, Elsevier Sciense Publishers Ltd (UK) 181-185 (Exhibit NOR-104); Traavik T. 1999. "Too early may be too late". Research report for DN, No 1999-1 (ISBN 82-7072-304-5) (Exhibit NOR-48)

[31] Traavik T. 1999. "Too early may be too late". Research report for DN, No 1999-1 (ISBN 82-7072-304-5) (Exhibit NOR-48)

[32] Droege M. *et al.*, 1998 (Exhibit NOR-105); Nielsen K. M. *et al.*, 2000 (Exhibit NOR-106), 2003 (Exhibit NOR-76)

ii) What type of consequences may this have in resistance development of pathogenic bacteria in the future?

54. We know that the amount of resistance genes is increasing dramatically when millions of tons of modified plant material will be harvested every year. The possible negative implications will most probably depend on the resistance genes in question and whether that antibiotic is used in therapeutic treatment or may be used in the future. There are also complex mechanisms for selection and spread of resistance genes within and between micro-organisms, where multi-resistance linked to bacteria plasmids transferred between microorganisms may play an important part (see Chapter 2.2.2.2.9 for further explanation).

2.2.2.2 Public and animal health concerns

2.2.2.2.1 Introduction

55. In the specific context of food safety assessment ”hazard” may be defined as a biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.

56. The hypothetical hazards of whole GM foods, i.e. those hazards that have been realized so far, fall into a few broad categories. All these realized hazards are either related to the inaccurate integration of transgenes into recipient plant genomes, uncertainty with regard to direct or indirect effects of the polypeptide product of the transgene, or uncertainty with regard to DNA types and circumstances promoting uptake and organ establishment of foreign DNA from mammalian gastro-intestinal tracts[33].

57. The following scientific concerns have been raised in connection with public and animal health. Some of the concerns will also be relevant for environmental risk assessments of GMOs due to the fact that the processes can take place in the environment:

[33] For a recent, authoritative review: see The Royal Society of Canada. 2001. Elements of Precaution: Recommendations for the regulation of food biotechnology in Canada. An expert panel report on the future of food biotechnology prepared by the Royal Society of Canada at the request of Health Canada, Canadian Food Inspection Agency and Environment Canada (ISBN 0-920064-71-x) (Exhibit NOR-22)

- Insufficient studies on putative effects of GM nucleic acids or food/feed on potential animal or human consumers
- Are the transgene DNA sequences given in the notifications the same as the insert sequences found in the GMPs?
- Persistence and uptake of DNA and proteins from mammalian GIT (gastro intestinal tractus).
- Transgenic or altered host cell proteins.
- Production of chemicals and pharmaceuticals in plants

2.2.2.2.2 GM feeding experiments

58. In spite of the obvious need, very few studies designed to investigate putative effects of GM nucleic acids or food/feed on potential animal or human consumers have been published in peer-reviewed journals[34]. A consensus has emerged that the effects observed in some published studies[35] must be experimentally followed up.

59. Most of the animal feeding studies performed so far has been designed exclusively to reveal husbandry production differences between GMOs and their unmodified counterparts. The few studies that have been designed to reveal physiological or pathological differences are extremely few, and they demonstrate a quite worrisome trend[36]: Studies performed by the industry find no differences, while studies from independent research groups reveal differences that should have merited immediate follow-up, confirmation and extension, which has not been the case.

2.2.2.2.3 Are the transgene DNA sequences given in the notifications the same as the inserted sequences found in the GMPs?

60. If the transgene DNA sequences given in the notifications differ from the inserted sequences found in the GMPs, the risk assessments made prior to approval of the GMPs for marketing do not necessarily cover the potential risks associated with the GMPs.

[34]Jose L. Domingo (2000). "Health Risks of GM Foods: Many Options but Few Data". Science, vol 288 Issue 5472, 1748-1749, 9 June 2000 (Exhibit NOR-29)

[35] i.e. Fares and El-Sayed, 1998; "Fine structural changes in the Ileum of mice fed on Endotoxin-treated Potatoes and Transgenic Potatoes" Natural Toxins, Vol. 6, Issue 6, pages 219-233 (Exhibit NOR-25); Ewen and Pusztai, 1999; "Effect of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine". The Lancet, Vol. 354, 16 October 1999. (Exhibit NOR-24)

[36]Pryme and Lembcke, 2003. " In vivo studies on possible health consequences of genetically modified food and feed--with particular regard to ingredients consisting of genetically modified plant materials". Nutr Health. 2003;17(1):1-8. (Exhibit NOR-66)

61. In all GMPs that have been carefully analyzed so far, the transgenic inserts found in the plants are rearranged compared to the notified construct sequences. The most thoroughly studied transgenic events are:

- Bt-transgenic maize Mon810
- Bt- and glufosinate-transgenic maize Bt176
- Glyphosate-transgenic maize GA21
- Glufosinate-transgenic maize T25 (Liberty Link)
- Glyphosate-transgenic soybean GTS 40-3-2

62. The nature of the rearrangements vary, and deletions (Mon810, GA21, Bt176), recombination's (T25, GTS 40-3-2, Bt176), tandem or inverted repeats (T25, GA21, Bt176) as well as rearranged transgene fragments scattered through the genome (Mon810) have been reported[37]. The transgenic modification techniques are prone to introduce such rearrangements because exogenous DNA transfer in plants elicits a "wound" response which activates nucleases and DNA repair enzymes. This may result in either degradation of the incoming DNA, or insertion of rearranged copies into the plant DNA[38]. In addition, the DNA constructs used to make transgenic plants may influence the rearrangement tendencies for a given transgenic event. Some genetic elements in the constructs may act as hotspots and elicit recombination's at high frequencies[39].

[37] Hernandez et al., 2003. "A specific real-time quantitative PCR detection system for event MON810 in maize YieldGuard based on the 3'-transgene integration sequence". Transgenic Research 12: 179-189, 2003 (Exhibit NOR-33); Holck et al., 2002. "5'-Nuclease PCR for quantitative event-specific detection of the genetically modified MON810 MaisGard maize". Eur Food Res Technol (2002) 214: 449-453 (Exhibit NOR-27); Collonnier et al., 2003. "Characterization of commercial GMO-inserts: A source of useful material to study genome fluidity?" (Exhibit NOR-75) ; Windels et al., 2001. "Characterisation of the Roundup Ready soybean insert". Eur Food Res Technol (2001) 213: 107-112 (Exhibit NOR-74); Rönning et al., 2003. "Event specific real-time quantative PCR for genetically modified Bt11 maize" (Zea Mays). Eur Food Res Technol (2003) 216: 347-354. (Exhibit NOR-68)

[38] Takano et al., 1997. "The structures of integration sites in transgenic rice". The Plant Journal 1997, 11(3), 353-361 (Exhibit NOR-30); Collonnier et al., 2003. "Characterization of commercial GMO-inserts: A source of useful material to study genome fluidity?" (Exhibit NOR-75). - In addition to cellular mechanisms controlling the transgene integration, subsequent selection procedures of the GM material may introduce further genomic reorganisations (Hernandez et al., 2003. "A specific real-time quantitative PCR detection system for event MON810 in maize YieldGuard based on the 3'-transgene integration sequence". Transgenic Research 12: 179-189, 2003 (Exhibit NOR-33)).

[39] This is the case for the 35S CaMV promoter that is present in most GMPs marketed so far, and also for the Ti plasmid of Agrobacterium tumefasciens and the nos terminator (Kohli et al., 1999. "Molecular characterization

63. While it was earlier assumed that integration of transgenic constructs took place at random locations in the recipient plant genome, it has now become evident that there are preferred integration sites in elements such as retrotransposons (T25, Mon810, GA21) and repeated sequences (Bt11 maize)[40]. Transgene insertions into, or close to, such genetic plant elements may lead to altered spatial and temporal expression patterns of plant genes in the proximity of the insert. Secondly, a strong retrotransposon LTR promoter may upregulate the transgene expression level. Thirdly, defective retrotransposons may start "jumping" under the influence of transacting factors recruited by the insert[41]. All these events may have unpredictable effects on the long-term genetic stability of the GMOs, as well as on their nutrional value, allergenicity and toxicant contents. These putative processes represent areas of omitted research with regard to health effects of GMOs.

2.2.2.2.4 Persistence and uptake of DNA and proteins from mammalian GIT (gastro intestinal tractus).

64. If DNA and proteins from GMPs persist in, and are taken up from mammalian GIT, this could, as will be further explained below, ultimately lead to inter alia cancer. The fate and consequences of DNA persistence and uptake is however not extensively studied, and this is therefore yet another area of uncertainties connected to GMPs.

65. It has generally been claimed that DNA and proteins are totally degraded in mammalian GITs. This has been based on assumptions that had never been systematically examined[42]. A restricted number of recent publications have demonstrated that foreign DNA and also

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of transforming plasmid rearrangements in transgenic rice reveals a recombination hotspot in the CaMV 35S promoter and comfirms the predominance of microhomoloy mediated recombination". The Plan Journal (1999) 17(6), 591-601 (Exhibit NOR-58); Collonnier et al., 2003. "Characterization of commercial GMO-inserts: A source of useful material to study genome fluidity?" (Exhibit NOR-75)). Hot spots may lead to tandem transgene repeats with interspersed plant DNA sequences in a single genetic locus. Presence of several inserts may also result from multimerisation in the plasmid before transformation or from multiple insertions.

[40] Rönning et al., 2003. "Event specific real-time quantative PCR for genetically modified Bt11 maize" (Zea Mays). Eur Food Res Technol (2003) 216: 347-354. (Exhibit NOR-68)

[41] Jank and Halsberger, 2000. "Recombinant DNA insertions into plant retrotransposons". Tibtech August 2000, volume 18, page 326 (Exhibit NOR-51)

[42] Palka-Santani et al., 2003. "The gastrointestinal tract as the portal of entry for foreign macromolecules: fate of DNA and proteins". Mol Gen Genomics (2003) 270:201-215 (Exhibit NOR-63)

proteins may escape degradation, to persist in the GIT and even to be taken up from the intestines and transported by the blood to internal organs in biologically meaningful versions[43]. These findings should not have come as such a surprise, since scientific articles from the 1990ies[44] strongly indicated that this was an area of omitted research, as stated by a number of reports[45].

66. Briefly summarised, the present conception of DNA persistence and uptake includes the persistence of ingested DNA in long fragments that are shed in the faeces. DNA may be detected in intestinal wall, peripheral white blood cells, liver, spleen and kidney, and the foreign DNA may be found integrated in the recipient genome. When pregnant animals are fed foreign DNA, fragments may be traced to small cell clusters in fetuses and newborns. The state of GIT filling, and the feed composition may influence DNA persistence and uptake. Complexing of DNA with proteins or other macromolecules may protect against degradation.

67. So far only two published reports have investigated the fate of foreign/transgenic DNA in humans[46]. The consequences of DNA persistence and uptake thus represent another area

[43]Schubbert et al., 1994. "Ingested foreign (phage M13) DNA survives transiently in the gastrointestinal tract and enters the bloodstream of mice". Mol Gen Genet. 1994 Mar;242(5):495-504 (Exhibit NOR-70), Schubbert et al., 1997, 1998 (Exhibit EC-13 and EC-14); Hohlweg and Doerfler, 2001. "On the fate of plants or other foreign genes upon the uptake in food or after intramuscular injection in mice". Mol Genet Genomics (2001) 265: 225-233 (Exhibit NOR-46); Palka-Santani et al., 2003. "The gastrointestinal tract as the portal of entry for foreign macromolecules: fate of DNA and proteins". Mol Gen Genomics (2003) 270:201-215 (Exhibit NOR-63); Einspanier et al., 2001. "The fate of forage plant DNA in farm animals; a collaborative case-study investigating cattle and chicken fed recombinant plant material". Eur Food Res Technol (2001) 212:129-134 (Exhibit NOR-31); Klotz et al., 2002. "Degradation and possible carry over of feed DNA monitored in pigs and poultry". Eur Food Res Technol (2002) 214:271-275 (Exhibit NOR-34); Forsman et al., 2003. "Uptake of amplifiable fragments of retrotranspon DNA from the human alimentary tract". Mol Gen Genomics (2003). 270:362-368 (Exhibit NOR-37); Chen et al., 2004. “Transfection of mEpo gene to intestinal epithelium in vivo mediated by oral delivery of chitosan-DNA nanoparticles”. World Journal of Gastroenterology 2004; 10(1):112-116 (Exhibit NOR-110); Phipps et al., 2003. " Detection of transgenic and endogenous plant DNA in rumen fluid, duodenal digesta, milk, blood, and feces of lactating dairy cows". J Dairy Sci. 2003 Dec;86(12):4070-8 (Exhibit Nor-64)

[44] Wolff et al., 1990. "Direct Gene Transfer into Mouse muscle in vivo". Science New Series Vol 247, No. 4948, page 1465 (Exhibit NOR-50); Jones et al., 1997. " Oral delivery of poly(lactide-co-glycolide) encapsulated vaccines". Behring Inst Mitt. 1997 Feb;(98):220-8 (Exhibit NOR-53)

[45] i.e. Traavik, 1999a. "An Orphan in science". Research Report for DN No. 1999-6 (Exhibit NOR-47)

[46] Forsman et al., 2003. "Uptake of amplifiable fragments of retrotranspon DNA from the human alimentary tract". Mol Gen Genomics (2003). 270:362-368 (Exhibit NOR-37);Netherwood et al., 2004. "Assessing the survival of transgenic plant DNA in the human gastrointestinal tract". Nature Biotechnology , Volume 22, No. 2, February 2004 (Exhibit NOR-36). In the former study, volunteers were fed rabbit meat. Rabbit retrotransposon sequences (RERV-H) were detected in the blood stream and in peripheral white blood cells for a considerable

of omitted research. Extrapolating from a number of experiments in mammalian cell cultures and in experimental animals, it is conceivable that in some instances insertion of foreign DNA may lead to alterations in the methylation and transcription patterns of the recipient cell genome. Furthermore, even small inserts may result in a so-called "destabilisation" process, the end-point of which may be malignant cancer cells.

68. The BSE/new variant Creutzfeld-Jacob's disease epidemics caused by the prion proteins painfully illustrated the phenomenon of protein persistence, uptake and biological effects. Two recent publications indicate this phenomenon may be more general that realized[47].

69. The consequences of protein persistence and uptake will vary with the actual situation. Generally spoken there is a possibility that toxic, immunogenic/allergic or carcinogenic molecules may gain entry to the organism via cells in the gastrointestinal walls. The persistence of Cry1Ab in faeces means a potential for spread on the fields through manure. The ecological effects, e.g. on insect larvae and earthworms[48] is at the moment an issue of shear speculation.

2.2.2.2.5 Transgenic or altered host cell proteins.

70. Transgenes or upregulated plant genes may give rise to toxicants, anti-nutritients, allergens and, putatively, also carcinogenic or co-carcinogenic substances. The concentration of a given transgenic protein may vary according to the location(s) of inserted construct DNA, and to environmental factors influencing the activity of the transgene regulatory elements, i.e. the 35S CaMV promoter. The biological effects of a given transgene protein, i.e. the Cry1Ab Bt-toxin, may be unpredictably influenced by

length of time after ingestion. In the latter study volunteers were fed epsps-transgenic (glyphosate-tolerant) soy as burgers and soy-milk. The transgenic DNA was detected in the small intestinal contents and bacteria.

[47] *The first (*Palka-Santani et al., 2003. "The gastrointestinal tract as the portal of entry for foreign macromolecules: fate of DNA and proteins". Mol Gen Genomics (2003) 270:201-215 (Exhibit NOR-63)*),* based on feeding of gluthathione-S-transferase to mice, demonstrated undegraded protein in stomach/small intestinal contents, and trace amounts in kidney extracts, 30 minutes or more after feeding. And, very significantly, incubation with stomach contents of control mice resulted in faster degradation than in feeding experiments. The second study concerned cattle fed cry1ab-transgenic maize Bt176 Einspanier et al., 2001. "The fate of forage plant DNA in farm animals; a collaborative case-study investigating cattle and chicken fed recombinant plant material". Eur Food Res Technol (2001) 212:129-134 (Exhibit NOR-31)*). Cry1Ab protein was detected in all parts of the GIT, and it was still detectable in the faeces.*

[48] Zwahlen C. *et al.*, 2003 (Exhibit NOR-97)

posttranslational modifications, alternative splicings, chimeric reading frames as a result of integration into the reading frame of a plant gene, and complex formation with endogenous plant proteins.

71. The influence of foreign DNA insertion on endogenous plant gene expression patterns may vary with local environmental factors, the actual insertion site(s), the number and stability of the inserts, transgene promoter effects, methylation patterns of the insert(s), and posttransformational mutations in the transgene protein coding as well as in regulatory sequences. Even a single nucleotide change may affect the properties of a protein, or it may create a new transcription factor binding motif.

72. One of the major health concerns related to GMPs is that the transgenic product itself, e.g. a Bt toxin, or upregulation of endogenous plant genes may result in *allergenic* compounds. The risk assessment of allergens is based on so-called *allergenicity decision trees*[49] .

73. Another important question related to allergenicity is whether postmarketing surveillance can provide useful information about allergens in GMO foods. For a number of reasons this is not likely to happen[50]. Treatment of allergy is symptomatic, whatever the cause may be. The allergenic case is often isolated, and the potential allergen is seldom identified. The number of allergy-related medical visits is not tabulated. Even repeated visits due to well-known allergens are not counted as part of any established surveillance system. Thus, during the October 2000 Starlink episode, it proved very difficult to evaluate Starlink (Containing Bt-toxin Cry9C) as a human allergen[51]. An additional reason for this was that the ELISA tests, used by FDA, that found no anti-Cry9C antibodies in suspected human cases were dubious because bacterial, recombinant antigens were used instead of the Cry9C maize versions that the individuals had been exposed to.

[49] Bernstein et al., 2003. "Clinical and Laboratory Investigation of Allergy to Genetically Modified Foods". Genetically Modified Foods, Mini-Monograph, Volume 111, No. 8, June 2003 (Exhibit NOR-39)

[50]Bernstein et al., 2003. "Clinical and Laboratory Investigation of Allergy to Genetically Modified Foods". Genetically Modified Foods, Mini-Monograph, Volume 111, No. 8, June 2003 (Exhibit NOR-39)

2.2.2.2.6 Bt toxins in Bt-transgenic GMOs

74. It is very important to be aware of the fact that the Bt-toxins expressed in GMOs have never been carefully analysed, and accordingly, their characteristics and properties are not known. What is clear from the starting point, however, is that they are vastly different from the bacterial *Bacillus thuringiensis* protoxins, used in organic and traditional farming and forestry for decennia[52]. The difference is evident already at the gene level, since the versions found in GMOs are genetically engineered to produce active Bt toxins. By extrapolation these have a number of potentially unwanted biological characteristics, ranging from solubilization and effects on insect and mammalian cells, to persistence and non-target effects in the environment[53]. In addition, the posttranslational modifications that may influence conformations, cellular targets and biological effects of GMP-expressed Bt-toxins are unknown.

75. During the last few years a number of observations that may be conceived as "early warnings" of potential health and environmental risks, have appeared in the literature[54].

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51 Bucchini and Goldman, 2002 (Exhibit EC-11)

52 Stotzky, 2000

53 Andow, 2002

54 Human and monkey cells exposed to Bt-toxins from the extra- or intra-cellular environment are killed or functionally disabled (Taybali and Seligy, 2000. "Human Cell Exposure Assays of Bacillus Thuringiensis Commercial Insecticides: Production of Bacillus cereus-like Cytolytic Effects from Outgrowth of Spores". Environmental Health Perspectives online, 18 August 2000 (Exhibit NOR-121)); Tsuda et al., 2003. "Cytotoxic activity of Bacillus Thuringiensis Cry proteins on mammalian cells transferred with cadherine-like Cry receptor gene of Bombyx mori (silkworm)" Biochemical Journal (2003) 369: 697-703(Exhibit NOR-72); Namba et al., 2003. "The cytotoxicity of Bacillus Thuringiensis subsp. coreanensis A 1519 strain against the human leukemic T cell". Biochimica et Biophysica Acta 1622 (2003) 29-35 (Exhibit NOR-61)). Influenza A infections in mice were changed from silent to lethal encounters by co-exposing the animals to Bt-toxin (Hernandez et al., 2000. "Super-infection by Bacillus Thuringiensis H34 or 3a3b can lead to death in mice infected with the influenza A virus". FEMS Immunology and Medical Microbiology 29 (2000), 177-181 (Exhibit NOR-120)**).** Farmworkers exposed to Bt spores developed IgG and IgE antibodies to Bt-toxin (Cry1Ab) (Taylor et al., 2001. "Will genetically modified foods be allergenic?" Journal of Allergy and Clinical Immunology, May 2001, 765-771 (Exhibit NOR-118)). The Bt-toxin Cry1Ac were found to have very strong direct and indirect immunological effects in rodents Vazquez et al., 1999. "Characterization of the mucosal and systemic immune response induced by Cry1Ac protein from Bacillus Thuringiensis HD 73 in mice". Brazilian Journal of Medical and Biological Research (2000) 33: 147-155 (Exhibit NOR-73); Moreno-Fierros et al.,2000. "Intranasal, rectal and intraperitoneal immunization with protoxin Cry1Ac from bacillus thuringiensis induces compartmentalized serum, intestinal, vaginal and pulmonary immune response in Balb/c mice". Microbes and infection 2, 2000, 885-890 (Exhibit NOR-38) , Moreno-Fierros et al, 2002. "Slight influence of the estrous cycle stage on the mucosal and systemic specific antibody response induced after vaginal and intraperitoneal immunization with protoxin CryA1c from bacillus thuringiensis in mice". ELSEVIER Life Sciences 71 (2002) 2667-2680 (Exhibit NOR-119). Earthworms exposed to Bt toxin Cry1Ab experience weight loss Zwahlen et al., 2003. "Effects of transgenic Bt corn litter on the earthworm Lumbricus terrestris". Molechular Echology (2003) 12, 1077-1086 (Exhibit NOR-116). Cattle fed the Bt176 maize variety demonstrated undegraded Cry1Ab through the whole alimentary tract, and the intact toxin was shed in faeces (Einspanier et al., 2004. "Tracing residual recombinant

2.2.2.2.7 Transgenic, glyphosate-tolerant (Roundup Ready) GMOs

76. These GMOs have an inserted transgene, *cp4 epsps*, coding for an enzyme which degrades the herbicide glyphosate. A very restricted number of experimental studies have been devoted to health or environmental effects of the GMOs or the herbicide. Some of these may be considered "early warnings" of potential health and environmental risks, and they should be rapidly followed up to confirm and extend the findings[55].

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feed molecules during digestion and rumen bacterial diversity in cattle fed transgene maize". Eur Food Res Technol (2004) 218:269-273 (Exhibit NOR-32)). Cry1Ab is much more resistant to degradation under field soil conditions than earlier assumed (Zwahlen et al., 2003. "Degradation of the Cry1Ab protein within transgenic Bacillus thuringiensis corn tissue in the field". Molecular Ecology (2003) 12, 765-775 (Exhibit NOR-117). Potentially IgE-binding epitopes have been identified in two Bt-toxins (Kleter and Peijnenburg, 2002. "Screening of transgenic proteins expressed in transgenic food crops for the presence of short amino acid sequences identical to potential IgE-binding linear epitopes of allergens". BMC Structural Biology, 12 December 2002, page 1 (Exhibit NOR-54)), and it should be added that many IgE-binding epitopes are conformationally,not linearly determined. Finally, it is a matter of concern that Bt-toxins have lectin characteristics (Akao et al., 2001. " Specificity of lectin activity of Bacillus thuringiensis parasporal inclusion proteins". J Basic Microbiol. 2001;41(1):3-6 (Exhibit Nor-42)). Lectins are notorious for finding receptors on mammalian cells. This may lead to internalization and intracellular effects of the toxins.
Occupational exposure to novel proteins, and potential allergic sensitization, has had little study, but could be of public health significance. An amazing number of foods have been proven to evoke allergic reactions by inhalation (Bernstein et al., 2003. "Clinical and Laboratory Investigation of Allergy to Genetically Modified Foods". Genetically Modified Foods, Mini-Monograph, Volume 111, No. 8, June 2003 (Exhibit NOR-39)). In this connection the findings of serum IgG/IgE antibodies to *B. thuringiensis* spore extracts (Bernstein et al., 1999. "Immune Responses in Farm Workers after Exposure to Bacillus Thuringiensis Pesticides". Environmental Health Perspectives Volume 107, No. 7, July 1999 (Exhibit NOR-40), Bernstein et al., 2003. "Clinical and Laboratory Investigation of Allergy to Genetically Modified Foods". Genetically Modified Foods, Mini-Monograph, Volume 111, No. 8, June 2003 (Exhibit NOR-39)) in exposed farm workers should be given further attention. Inhalant exposure to Bt-toxin containing GMP materials may take place through pollen in rural settlements and also through dust in workplaces where foods are handled or processed.

[55] Mice fed GM soybean demonstrated significant morphological changes in their liver cells (Malatesta et al., 2002. "Ultrastructural Morphometrical and Immunocytochemical Analysis of Hepatocyte Nuclei from Mice fed on Genetically Modified Soy Bean". Cell Structure and Function 27: 173-180 (2002) (Exhibit NOR-59)). The data suggested that *epsps*-transgenic soybean intake was influencing livercell nuclear features in both young and adult mice, but the mechanisms responsible for the alterations could not be identified by the experimental design of these studies.

Treatment with glyphosate (Roundup) is an integrated part of the *epsps*-transgenic GMP application. A number of recent publications indicate unwanted effects of glyphosate on aquatic (Solomon and Thompson 2003. " Ecological risk assessment for aquatic organisms from over-water uses of glyphosate". J Toxicol Environ Health B Crit Rev. 2003 May-Jun;6(3):289-324 (Exhibit NOR-71) and terrestric (Ono et al., 2002. " Inhibition of Paracoccidioides brasiliensis by pesticides: is this a partial explanation for the difficulty in isolating this fungus from the soil?". Med Mycol. 2002 Oct;40(5):493-9 (Exhibit NOR-62), Blackburn and Boutin, 2003. "Subtle Effects of Herbicide Use in the Context of Genetically Modified Crops: A Case Study with Glyphosate (Roundup)". Ecotoxicology, 12, 271-285, 2003 (Exhibit NOR-111)) organisms and ecosystems. Recent studies in animals and cell cultures point directly to health effects in humans as well as rodents and fish. Female rats fed glyphosate during pregnancy demonstrated increased foetal maortality and malformations of the skeleton (Dallegrave et al., 2003; "The teracogenic potential of the herbicide glyphosate Roundup in Wistar rats". Toxicology letters 142 (2003), 45-52 (exhibit NOR-23). Nile Tilapia

2.2.2.2.8 35S CaMV promoter

77. Cauliflower mosaic virus (CaMV) is a DNA-containing para-retrovirus replicating by means of reverse transcription (Poogin et al., 2001). One of the viral promoters, called 35S is a general, strong plant promoter. It has been used to secure expression of the transgenes in most of the GMOs commercialized so far. Besides studies in yeast[56] and in *Schizosaccharomyces pomb*[57]*e* there are, however, published studies indicating that the 35S CaMV promoter might have potential for transcriptional activation in mammalian systems[58].

(*Oreochromis niloticus)* fed sublethal concentrations of Roundup exhibited a number of histopathological changes in various organs (Jiraungkoorskul et al., 2003. " Biochemical and histopathological effects of glyphosate herbicide on Nile tilapia". Environ Toxicol. 2003 Aug;18(4):260-7 (Exhibit NOR-52)). A study of Roundup effects on the first cell divisions of sea urchins (Marc et al., 2002. "Pesticide Roundup provokes cell division dysfunction at the level of CDK1/Cyklin B Activation". Chem. Res. Toxicol. 2002, 15, 326-331 (Exhibit NOR-49)) is particular interest to human health. The experiments demonstrated cell division dysfunctions at the level of CDK1/Cyclin B activation. Considering the universality among species of the CDK1/Cyclin B cell regulator, these results wuestion the safety of glyphosate and Roundup on human health. In another study (Axelrod et al., 2003. "The effect of acute pesticide exposure on neuroblastoma cells chronically exposed to diazinon". Toxicoloy 185 (2003) 67-78 (Exhibit NOR-45)) in was demonstrated a negative effect of glyphosate, as well as a number of other organophosphate pesticides, on nerve-cell differentiation.

[56] Hirt et al., 1990

[57] Gmunder and Kohli, 1989. " Cauliflower mosaic virus promoters direct efficient expression of a bacterial G418 resistance gene in Schizosaccharomyces pombe". Mol Gen Genet. 1989 Dec;220(1):95-101. (Exhibit NOR-43); Probjecky et al., 1990. " Expression of the beta-glucuronidase gene under the control of the CaMV 35s promoter in Schizosaccharomyces pombe". Mol Gen Genet. 1990 Jan;220(2):314-6 (Exhibit NOR-65)

[58] The promoter initiates transcription in rabbit reticulocyte lysate (Ryabova and Hohn, 2000. "Ribosome shunting in the cauliflower mosaic virus 35S RNA leader is a special case of reinitiation of translation functioning in plant and animal systems". Genes & Development 14:817-829 (2000) (Exhibit NOR-69)) and in Xenopus oocytes (Ballas et al., 1989. "Efficient functioning of plant promoters and Poly(A) sites in Xenopus oosytes". Nucleic Acids Research Vol 17 Issue 19 7891-7903 1989 (Exhibit NOR-41)). In the latter studies it was found that circular, supercoiled 35S CaMV driven expression plasmids were more active than linear forms. The CaMV genome carries structural and functional resemblance to mammalian *Retroviridae* and to *Hepadnaviridae*, which contains the human hepatitis B virus (HBV). A 19 bp palindromic sequence, including the TATA box of the 35S CaMV promoter, may act as a recombination hotspot in plants (Kohli et al., 1999. "Molecular characterization of transforming plasmid rearrangements in transgenic rice reveals a recombination hotspot in the CaMV 35S promoter and comfirms the predominance of microhomoloy mediated recombination". The Plan Journal (1999) 17(6), 591-601 (Exhibit NOR-58)), and it is unknown whether this is also the case in mammalian cells. In a recent review article (Ho et al., 2000. "Hazardous CaMV promoter?". Nature Biotechnology volume 18, April 2000 (Exhibit NOR-26)) it was hypothesized that the 35S CaMV promoter might represent health hazards to human and animal consumers of transgenic plant materials. Against this it was argued that humans and mammals are continuously being exposed to CaMV particles through infected plant materials. This is true enough, but it is then forgotten that there are documented examples of animal species being resistant to intact viruses, but highly susceptible to infection by DNA from the same virus (Refs: Rekvig et al., 1992. " Antibodies to eukaryotic, including autologous, native DNA are produced during BK virus infection, but not after immunization with non-infectious BK DNA". Scand J Immunol. 1992 Sep;36(3):487-95 (Exhibit NOR-67); Zhao et al., 1996. ”Infectivity of chimeric human T-cell leukaemia virus type I molecular clones assessed by naked DNA inoculation”. Procedures of National Academy of Sciences, USA, Vol. 93, pp. 6653-

2.2.2.2.9 Implications of Kanamycin resistance genes (e.g. *nptII*)

78. The antibiotic kanamycin is used extensively in crop genetic engineering as a selectable marker, inter alia in GM oilseed rape lines MS1Bn x RF1Bn and Topas 19/2, which are at issue in this case.

79. A selectable marker is a gene inserted into a cell or organism to allow the modified form to be selectively amplified while unmodified organisms are eliminated. In crop genetic engineering the selectable marker is used in the laboratory to identify cells or embryos that carry the genetic modifications that the engineer wishes to commercialize. The selection gene is used once briefly in the laboratory, but thereafter the genetically modified (GM) crop has the unused marker gene in each and every one of its cells.

80. There is a well known cross resistance between antibiotics of a particular type. A mutation to resistance to an antibiotic may cause resistance to some or all of the members of the antibiotic family. Kanamycin is a member of the family aminoglycoside antibiotics. Cross resistance between Kanamycin and other aminoglycosides including streptomycin, gentamycin and tobramycin was found to vary markedly between isolates[59]. All of the antibiotics mentioned are used to treat human diseases.

81. Along with cross resistance to aminoglycoside antibiotics, pathogenic bacteria frequently develop multiple drug resistance transmitted on a single plasmid[60]. Pathogenic bacteria do aquire plasmids with multiple antibiotic resistance genes in areas where the antibiotics are used extensively.

6658, June 1996, Medical Sciences (Exhibit NOR-112; reviews: Traavik, 1999a"An Orphan in science". Research Report for DN No. 1999-6; (Exhibit NOR-47);(Ho et al., 2000. "Hazardous CaMV promoter?". Nature Biotechnology volume 18, April 2000 (Exhibit NOR-26))).

[59] The aminoglycoside antibiotic neomycin was found to cross react with kanamycin B in inhibiting RNase P ribozyme 16s ribosomal RNA and tRNA maturation (Mikkelsen et al., 1999. "Inhibition of RNase P RNA cleavage by aminoglycosides". National Academy of Sciences, USA, Vol. 96, page 6155-6160, May 1999 (Exhibit NOR-60).

[60] For example, the cholera pathogen *Vibrio cholerae*, first isolated from India, Bangladesh and Thailand (Yamamoto et al., 1995. "Emergence of tetracycline resistance due to a multiple drug resistance plasmid in Vibrio cholerae O139". FEMS Immunology and Medical Microbiology 11 (1995) 131-136 (Exhibit NOR-114)**)** was found to have a plasmid resistant to tetracycline, ampicillin, chloramphenicol, kanamycin, gentamycin, sulphaethoazole and trimethoprim.

82. In spite of the belief of many genetic engineers that kanamycin is no longer employed in medical applications, there is evidence that the antibiotic is used extensively for some applications[61].

83. The possible consequences of the use of this antibiotic resistance marker gene are further commented upon below in Chapter 2.3.3.

2.2.2.2.10 Production of chemicals and pharmaceuticals in plants (Molecular plant pharming).

84. Production of chemicals and pharmaceuticals in plants could lead to unwanted and potentially harmful substances in food and feed through hybridisation between GMPs and closely related domesticated species or unintended mixture between such GMPs and conventional plants during the first steps of production.

85. There is a great commercial interest in the use of transgenic plants to produce drugs and industrial chemicals, in essence turning crops into biological factories. Enzymes, antibodies, human blood products, vaccines, hormones and other proteins for pharmaceutical and industrial purposes have already been designed, and hundreds of experimental releases with this type of gene modified plants have been conducted in USA the last twelve years[62]. These are proteins and substances that exhibit high levels of biological activities and are intended to be used for particular purposes under strict controlled circumstances.

[61] Kanamycin is used prior to endoscopy of colon and rectum (Ishikawa et al., 1999. "Prevention of infectious complications subsequent to endoscopic treatment of the colon and rectum". J Infect Chemother 1999, 5:86-90 (Exhibit NOR-28)) and to treat ocular infections (Hehl et al., 1999. " Improved penetration of aminoglycosides and fluorozuinolones into the aqueous humour of patients by means of Acuvue contact lenses". Eur J Clin Pharmacol. 1999 Jun;55(4):317-23 (Exhibit NOR-44)) It is used in blunt trauma emergency treatment (Yelon et al., 1996. "Efficacy of an intraperitoneal antibiotic to reduce the incidence of infection in the trauma patient: a prospective, randomized study". J Am Coll Surg. 1996 Jun;182(6):509-14. (Exhibit NOR-115) and has been found to be effective against *E coli 0157* without causing release of verotoxin (Ito et al., 1997)

[62] R. M. Twyman *et al*. 2003. "Molecular farming in plants; host systems and expression technology". Trends in Biotechnology (Exhibit NOR-35); Mellon M and J. Rissler, 2004. Report from: Union of Concerned Scientists, Gone To Seed – Transgenic Contaminants in the Traditional Seed Supply (www.ucsusa.org) (Exhibit NOR-6)

86. For safety reasons questions have been raised whether this type of gene modified plant production should be conducted with our traditional crop plants in open agricultural production without increased safety considerations. Many of the novel products in this new type of farming industry, can in many cases both be toxic and allergenic or biological active in humans and animals[63]. The choices of plant species used are in most cases the same as those used as food and feed species (e.g. maize, soybeans and oilseed rape).

87. The problems of cross pollination and hybridisation with conventional crops and wild relatives, together with unintended mixing through farming and the transport systems, demands a need for confined production and strict segregation that entails no mixing with plant products intended for food and feed. There is already a known example where pharmaceutical corn in experimental field release contaminated the soybean harvest in Nebraska, USA[64].

88. It is also an example from USA where the genetically modified maize variety StarLink that was only approved for animal feed, ended up in food products on the U.S. marked, and also contaminated the U.S. maize seed supply. Despite concerted effort, it has proved surprisingly difficult to purge the U.S. grain system of the contaminant, and the expenditures have been considerable. As recently as December 2003, StarLink was still reported in domestic grain in USA[65]. The example of StarLink shows clearly how difficult it may be in the future to get rid of possible more hazardous modified traits if they are spread to the seed supply and into different crop varieties for food use[66].

[63] B. Tokar, 2001 (Exhibit NOR-101)

[64] Press release November 2002, U.S. Department of Agriculture

[65] Lin et. al., 2001. "Star Link: Impacts on the U.S. Corn Market and World Trade". Feed Yearbook/FDS-2001/April 2001 page 46 (Exhibit NOR-91); Mellon M and J. Rissler, 2004. Report from: Union of Concerned Scientists, Gone To Seed – Transgenic Contaminants in the Traditional Seed Supply (www.ucsusa.org) (Exhibit NOR-6)

[66] B. Tokar, 2001 (Exhibit NOR-101)

2.3 Regulatory approaches to GMOs at national and international level

2.3.1 National regulatory approaches

89. As pointed out by the EC in paragraphs 71 – 86 of its first written submission, there are different regulatory approaches to GMOs throughout the world. The great majority of regulatory systems adopted so far requires some form of authorisation before a specific product, be it a GM crop or GM food, is marketed. Moreover, the granting of that authorisation is dependent on a case-by-case risk assessment of the individual product in question.

90. The Norwegian regulatory system, like that of the great majority of other national regulatory systems so far adopted, follows this approach. The production and marketing of GMOs require prior approval by the competent authorities, as provided for in Section 10 of the Act relating to the production and use of genetically modified organisms (the Gene Technology Act), which regulate all GMOs[67]. Risk assessment is the basic element in the Norwegian regulatory approach. Under Section 11 of the Gene Technology Act, applications for approval of the deliberate release shall contain an impact assessment setting out the risk of any detrimental effects on health and the environment as well as other consequences of the release.

2.3.2 International conventions and standard setting work in international organisations

91. As pointed out by the EU in their first written submission, Part II.B, the approaches taken in the great majority of national regulatory systems are illustrative of a global trend, which has led to the adoption of several international instruments to specifically address the risks of GMOs.

92. The Cartagena Protocol, which is a result of a multilateral reflection process initiated at the Earth Summit in Rio de Janeiro in June 1992, when the Convention on Biological Diversity was opened for signature, is among the most important instruments in this regard[68].

[67] English Translation of the Norwegian Act relating to the production and use of genetically modified organisms (Gene Technology Act; Act No. 38 of 2 April 1993 (Exhibit NOR-21)

[68] We refer to *EC First written submission,* Part II.B.Chapter 3 for a description of the Protocol.

93. As far as a description of the Cartagena Protocol and international conventions and standard setting work in international organisations is concerned, we refer to Part II, litra B, chapters 3 and 4 of the first written submission of the EC.

2.3.3 Conclusion

94. Norway fully subscribes to the conclusion drawn by the EU in paragraph 131 of its first written submission, in which it is stated that "[-] *national regulatory approaches to GMOs, while varying in a number of aspects, generally have in common that they require pre-market notification, risk assessment and approval. With the adoption of the Biosafety Protocol, the international Community has adopted binding rules on trade in GMOs. At the same time international consensus has been established on certain issues of risk assessment and risk management, and on the role of the precautionary principle in decision-making. Against this background the European Communities submits that it is not plausible to argue that GM products are – or should be treated as – equivalent to non-GM products.*"

2.4 Norwegian risk assessements on GMOs where certain EC Member States maintain national measures

2.4.1 Introduction

95. Norway will in the following explain in more detail its risk assessments regarding Bt.176, MS1xRF1 and Topas 19/2, which led to the decision of Norway to prohibit the marketing of these three GMOs.

2.4.2 Maize Line Bt 176

96. EC consent to market Maize Line Bt176 under Directive 90/220/EC was given 23 January 1997[69]. On the basis of a prior risk assessment Norway prohibited on 1 October 1997 Maize Line Bt176. In August 2000 the risk assessment of 1997 was revised. [70] The risk

[69] Commission Decision 97/98/EC (Exhibit NOR-13)

[70] See Basis for the Norwegian decision to prohibit marketing of genetically modified maize LINE Bt176 approved for marketing pursuant to council directive 90/220/EEC by The Directorate for Nature Management of Norway of August 2000, hereafter referred to as "The August 2000 Risk Assessment Report of Bt176" (Exhibit NOR-107)

assessement forms the basis for the Norwegian prohibition of 15 December 2000. It repeals the regulation of 1 October 1997 and at the same time replaces it with a renewed prohibition.[71] The regulation entered into force the same day.

97. The main reasons for the decisions to prohibit this GM maize were concerns related to the risks associated with a possible horizontal transfer of the *amp* gene for resistance to the antibiotic ampicillin contained in the product, and with ecological effects of the insect toxin encoded by the *cryIA (b)* genes. In the following these aspects will be further described.

2.4.2.1 Horizontal transfer of genes encoding antibiotic resistance according to Norwegian risk assessments on Bt 176 of 1997 and 2000.

98. Antimicrobial agents are the foundation of modern infectious disease treatment. The general observation that microorganisms can develop resistance to antibiotics has created a situation where these drugs are losing their effectiveness because of the spread and persistence of resistant microorganisms.

99. The *amp* gene inserted in the genetically modified maize line encodes a broad-spectrum β-lactamase that inactivates several β-lactam antibiotics including broad-spectrum penicillins such as ampicillin, amoxicillin and carbenecillin. These are all very important for treating various bacterial infections in human and veterinary medicine. The insertion of the *amp* gene into *Z. maize* therefore entails potential health and environmental impacts if the gene is transferred to bacteria.

100. A transfer of the *amp* gene to pathogenic bacteria in such a way that the gene is successfully incorporated and expressed would therefore be highly undesirable because it might impede clinical treatment.

101. As is documented in the attached risk assessment mentioned above, there are studies indicating that there is a risk for horizontal transfer of the *amp* gene. However, the mechanisms regulating putative horizontal gene transfer under natural conditions are

[71] Section 1 point 3 of Regulation No. 1268 of 12 December 2000 (Exhibit NOR-20)

inadequately described, and the information available does not allow the frequency of such events to be fully predicted.

102. In the risk assessment of August 2000, it was therefore concluded that further studies were required to elucidate the potential for transfer of antibiotic resistance genes from plants to microorganisms.[72] Although it was not yet known whether horizontal gene transfer might significantly increase the number of antibiotic resistant pathogenic bacteria, this the conclusion of the risk assessment was that this risk should be avoided for reasons of precaution.

103. Furthermore, as an important point, it was noted that newer technology was available which would avoid the presence of genes encoding antibiotic resistance in genetically modified plants.

2.4.2.2 Recent international developments concerning genes encoding antibiotic resistance

104. The concerns related to horizontal transfer of genes encoding antibiotic resistance are now also shared by Codex Alimentarius and the European Food Safety Authority:

105. At its 26th session in July 2003, the Codex Alimentarius Commission adopted the Draft Guideline for the Conduct of Food Safety assessment of Foods Derived from Recombinant-DNA Plants[73] elaborated by the Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology. According to Section 5 of this guideline, which concerns the use of antibiotic resistance marker genes, *"[-]Antibiotic resistance genes used in food production that encode resistance to clinically used antibiotics should not be present in foods [-]."* It is furthermore stated *that "[-] Alternative transformation technologies that do not result in antibiotic resistance marker genes in foods should be used in the future development of recombinant-DNA plants, where such technologies are available and demonstrated to be safe [-]."*

72 The August 2000 Risk Assessment Report of Bt176" (Exhibit NOR-107)

[73] ALINORM 03/41, para 52 and Appendix V, and ALINORM 03/34, Appendix III (Exhibit NOR-11)

106. On 2 April 2004 The Scientific Panel on Genetically Modified Organisms under the European Food Safety Authority (EFSA) adopted its opinion on the use of antibiotic resistance genes as marker genes in genetically modified plants[74]. The Panel conducted its evaluation in concordance with the Codex principles mentioned above. The Panel concluded that "[-] *the use of genes* [-] *which includes resistance to* [-] *ampicillin* [-], *should be restricted to field trial purposes and should not be present in GM plants to be placed on the market.*"

107. Consequently, the concerns related to the risks associated with a possible horizontal transfer of the *amp* gene for resistance to the antibiotic ampicillin contained in the GM maize Bt176, which led to the prohibition of the marketing of this product in these countries, are supported by the assessment made by the Scientific Panel on Genetically Modified Organisms under EFSA in accordance with the Codex principles mentioned above.

2.4.2.3 Ecological effects of the insect toxin encoded by the *cryIA (b)* genes

108. As stated above, the other main reason for the decision to prohibit the GM maize Bt176 was concerns related to the risks associated with ecological effects of the insect toxin encoded by the *cryIA (b)* genes. As is documented in the attached risk assessment mentioned above, there are indications that the toxin produced by these genes may also affect other organisms, and that the selection for target insects that are resistant to Bt toxins may be enhanced by the introduction of plants producing Bt toxins.

109. As shown by the following observation in the 2000 risk assessment the evidence of this is more evident than in the 1997 risk assessment: *"Most of these results [of the present risk assessment] do not introduce new arguments, but bring more insight into the aspects of the application that led to the Norwegian decision [of 1997]. The assessment of potential effects of the Bt toxin on non-target insects is, however, for the most part based on papers published after the Norwegian decision [of 1997."* (Underlining added)[75]

[74] "*Opinion of the Scientific Panel on Genetically Modified Organisms on the use of antibiotic resistance genes as marker genes in genetically modified plants (Question No EFSA-Q-2003-109)"*The EFSA Journal (2004) 48, 1-18. (Exhibit NOR-12)

2.4.3 Oilseed rape line MS1 x RF1

110. EC consent to market MS1 x RF1 under Directive 90/220/EEC was given on 6 February 1996.[76] After finalizing the risk assessment of this GM Maize, Norway decided to prohibit this GM maize on 1 October 1997.

111. In 2000 the risk assessment was revised.[77] The prohibition from 1997 to prohibit this GM Maize was maintained by decision of 15 December 2000.[78]

112. The main reasons for the decision to prohibit this GM oilseed rape line were concerns related to the risks associated with a possible horizontal transfer of the *nptII* gene for resistance to the antibiotics neomycin and canamycin contained in the product, and with the consequences of gene flow from the genetically modified oilseed rape to wild plants and crops.

2.4.3.1 Horizontal transfer of genes encoding antibiotic resistance according to Norwegian risk assessments on MS1 x RF1 of 1997 and 2000.

113. The same concerns as explained above Chapter 2.4.2 in relation to Bt 176 was cited by the risk assessments in 1997 and 2000 regarding MS1 x RF1. The resistance gene inserted in the genetically modified oilseed rape *(Brassica napus)* is the *nptII* gene, which encodes the enzyme neomycin phosphotransferase II (nptII). NptII gives the organism resistance to kanamycin and neomycin.

114. Transfer of this gene to pathogenic bacteria could contribute to worsen the problem of development of antibiotic resistance. When the risks of this particular genetically modified oilseed rape was assessed, some results indicated that there was a risk for horizontal transfer of the *nptII* gene. As with Bt 176, further studies were needed.

[75] The August 2000 Risk Assessment Report of Bt176" (Exhibit NOR-107)
[76] Commission Decision 96/158/EC (Exhibit NOR-15)
[77] See risk assessement"Genetically modified oilseed rape line MS1Bn x RF1 approved for marketing pursuant to Council Directive 90/220/EEC - Basis for the Norwegian decision to prohibit marketing" by Directorate for Nature Management, Norway. (Exhibit NOR-16)
[78] Regulation No. 1268 of 12 December 2000 (Exhibit NOR-20)

2.4.3.2 Recent international developments concerning genes encoding antibiotic resistance

115. The concerns related to horizontal transfer of genes encoding antibiotic resistance are in our opinion in line with the concerns which led to the adoption by the Codex Alimentarius Commission at its 26th session in July 2003 of the Draft Guideline for the Conduct of Food Safety assessment of Foods Derived from Recombinant-DNA Plants mentioned above in Chapter 2.4.2.2.

116. According to the opinion of the Scientific Panel on Genetically Modified Organisms of the European Food Safety Authority of 2 April 2004 mentioned above[79] "[-] *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.*"

117. Generally speaking there is a lack of research on existence of possible antibiotic resistance in different microbial communities in different environments. There is little knowledge regarding mechanisms of multi-resistance development and spread linked to GMO and possible harmful effects. There is no research, that we are aware of, on possible effects on humans and animals under treatment of antibiotics eating genetically modified food with antibiotic resistance markers.

118. According to Annex III of the Cartagena Protocol on Biosafety, which sets out more detailed guidance on risk assessment under Article 15 of the Protocol, *"[l]ack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk"*.

119. It should be noted that within the EU, a Working Group has been set up to consider the use of marker genes in GMOs. Its purpose is to consider possible adverse effects on

[79] "*Opinion of the Scientific Panel on Genetically Modified Organisms on the use of antibiotic resistance genes as marker genes in genetically modified plants (Question No EFSA-Q-2003-109)"*The EFSA Journal (2004) 48, 1-18. (Exhibit NOR-12)

human health and the environment stemming from GMOs, which contain genes expressing resistance to antibiotics.[80] This Working Group has not yet completed its work.

2.4.3.3 Consequences of gene flow from the genetically modified oilseed rape to wild plants and crops

120. The other main concern that led to the prohibition of GM oilseed rape line MS1 x RF1 in 1997 and 2000 was gene flow, or introgression of transgenes, from crops into wild plant populations. This is a major concern associated with the cultivation of genetically modified plants. The consequences of crop-to-wild gene flow may be a significant evolutionary change, as it threathens the extinction of the recipient species. For introgression to occur, the species involved must be cross-compatible and produce fertile hybrid offspring. The rate of cross-pollination is crucial for the hybridisation rate between cross-compatible species, and is dependent on factors such as the distance between the plants, the number of donor and recipient plants and the timing of flowering.

121. As is documented in the attached risk assessment[81], hybridisation between genetically modified oilseed rape and several wild and domesticated plant species in Norway is possible. Introgression of the gene conferring gluphosinate-tolerance into cross-compatible species could lead to the development of gluphosinate-resistant weeds. In addition, hybridisation with other crop plants could have undesirable effects such as future agricultural problems connected to weed management.

2.4.4 Oilseed rape line Topas 19/2

122. Unlike the two other GMOs discussed above, the Topas 19/2 was not prohibited in 1997. But after finalizing the risk assessment of Topas 19/2 in 2000, Norway decided to prohibit this GM on 15 December 2000.[82] The assessment of this GMO is summarized in a letter of 15 December 2000 to the Secretary of the EEA Joint Committee.[83] As can be

[80] Under Article 4(2) of Directive 2001/18/EC (Exhibition NOR-18) particular consideration shall be taken in relation to such GMOs

[81] See risk assessement"Genetically modified oilseed rape line MS1Bn x RF1 approved for marketing pursuant to Council Directive 90/220/EEC - Basis for the Norwegian decision to prohibit marketing" by Directorate for Nature Management, Norway. (Exhibit NOR-16)

[82] Regulation No. 1268 of 12 December 2000 (Exhibit NOR-20)

[83] "*Information on the Norwegian Decision on the placing on the market of genetically modified spring oilseed rape line Topas 19/2*",(Exhibit NOR-19)

seen from that document, the main reason [84]for prohibiting marketing of oilseed rape line Topas 19/2 is that it contains the *npt II* gene encoding resistance to the antibiotics kanamycin and neomycin. The assessments and comments with regard to antibiotic resistance marker genes in oilseed rape MS1xRF1 above are also applicable for oilseed rape line Topas 19/2.

3. LEGAL DISCUSSION

3.1 Introductory comments

123. As explained earlier, Norway will focus on certain aspects regarding the Complainants' third claim; namely the EC Member State national measures with regard to the three GMO-products Bt 176 and the two Oilseed Rape Lines MS1xRF1 and Topas 19/2.

124. The risk assessments – as described in detail in Chapter 2.4. above – on which the Norwegian decisions relating to these GMOs were based, may assist the Panel's understanding of some points of fact and law when reviewing the national measures of Austria, Germany, Luxembourg, France and Greece.[85]

3.2 The SPS Agreement is not applicable to measures against antibiotic resistance marker genes

[84] It should be added that already in 1996 Norway was also concerned with the usage of herbicide resistant crops. In letter of 19 July 1996 to the EC Commission the following concerns were raised: *"Assessment of the potential environmental and health impacts of the herbicide and its metabolites should form an integral part of the assessment of the herbicide resistant variety. We also would like to express our concern about the development of herbicide resistant crops as a main trend in agricultural biotechnology. Experiences with environmental chemical application, both in agriculture and in other areas, have shown that harmful effects on human health and on the environment are not easily assessed, and such effects are often discovered several years later. For instance, the synergistic effects of some common pesticides, are recently discovered. The pesticides dieldrine, endosulfane, toxaphene and chlordane are found to have up to 1000 times more estrogenic potency when two chemicals are mixed than any of the chemicals alone (S.F. Arnold et al. Science 272, 1489 (1996)).*"

[85] Austria prohibited maize Bt 176 on 14.02.97, Luxembourg on 17.03.97 and Germany on 04.04.00. France prohibited the Oilseed Rapes C/UK/94/M1/1 on 20.11.98. An import ban by Greece on C/UK/95/M5/1 was made 03.11.98 and prohibited in France on 20.11.98.

125. The definitions in Annex A point 1 are quite precise. The application of the SPS Agreement will depend on the purpose of each particular measure, and more specifically which risks a measure is intended to protect against.

126. If a particular objective is not covered by the SPS Agreement, a decision which invokes this particular risk shall not be assessed under SPS, but rather under the TBT Agreement or the GATT. Should the Panel decide that only one objective falls under the SPS, the remaining part of the decision must be assessed under the other Agreements.[86]

Article 1 of the *SPS Agreement* (entitled *General Provisions*) provides:

> 1. This Agreement applies to all sanitary and phytosanitary measures which may, directly or indirectly, affect international trade. Such measures shall be developed and applied in accordance with the provisions of this Agreement.
>
> 2. For the purposes of this Agreement, the definitions provided in Annex A shall apply.
>
> 3. The annexes are an integral part of this Agreement.
>
> 4. Nothing in this Agreement shall affect the rights of Members under the Agreement on Technical Barriers to Trade with respect to measures not within the scope of this Agreement.

Annex A of the *SPS Agreement* (entitled *Definitions*), point 1, provides in relevant parts:

> 1. Sanitary or phytosanitary measure – Any measure applied:
>
> (a) to protect animal or plant life or health within the territory of the Member from risks arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease-causing organisms;

[86] We refer also to the arguments presented by the EC in this respect in their first written submission para 441

> (b) to protect human or animal life or health within the territory of the Member from risks arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs;
>
> (c) to protect human life or health within the territory of the Member from risks arising from diseases carried by animals, plants or products thereof, or from the entry, establishment or spread of pests; or
>
> (d) to prevent or limit other damage within the territory of the Member from the entry, establishment or spread of pests.

127. There is a footnote (4) to Annex A to the *SPS Agreement* that states:

> For the purpose of these definitions, "animal" includes fish and wild fauna; "plant" includes forests and wild flora; "pests" includes weeds; and "contaminants" include pesticides and veterinary drug residues and extraneous matter.

128. As a point of departure, we note that according to the wording of Annex A, the protection from risks arising from GMOs or GM products *per se*, is not mentioned. This means that the objective(s) of a measure in relation to concrete risk(s), will decide whether a measure falls under Annex A, point 1.

129. Several concerns were raised in the Norwegian risk assessments of the three GMOs. The risks associated with the use of antibiotic resistance marker genes, were, however, the main justification for the bans. More specifically, and as explained in detail in Chapter 2.4 above, the concern was that the antibiotic resistant trait in the GM crop or product DNA might be transferred to bacteria, particularly in the digestive tract of humans or animals, and that this might negatively impact on clinical and veterinary medicine, which relies heavily on antibiotics (and therefore on the absence of resistance to antibiotics).

130. As explained by the EC[87] Plant DNA is in itself not an organism, although the plant within which it is contained is, as long as it is living. Even if the plant DNA would still be in an organism, and its ingestion would eventually contribute to the development of antibiotic resistance, it would not be the plant DNA that caused disease. The disease

[87] Ibid paras 431-432

would have to come from some other entirely independent source. The development of antibiotic resistance may make disease treatment more difficult, but it does not cause the disease itself. Plant DNA does not therefore fall within sub-paragraphs (a) or (b). It does not fall within sub-paragraphs (c) or (d) because it does not concern a pest.

131. In conclusion, the SPS Agreement is not applicable to the national bans insofar as their purpose is to safeguard against the risks of antibiotic resistance.

3.3 Alternative argument in respect of SPS Agreement Article 5.7

132. Should the Panel, nevertheless, decide to assess Member States' national measures regarding any of the three GMOs under the SPS Agreement, Norway will argue, in the alternative, that the measures against the risks of antibiotc resistance marker genes (ARMG) fully confrom to the SPS Agreement,- in particular Article 5.7 thereof.

133. The EC has convincingly shown that the national measures of Member States – if they are to be assessed under the SPS agreement – are "provisionally adopted". [88] This follows *inter alia* from the legal basis in internal EC law. We refer to the EC's first submission for further details.[89]

134. Since these Member States' measures are provisional, any evaluation of the conformity of the bans with the SPS agreement must be made under Article 5.7 and not under Article 5.1.

135. Article 5.7 of the SPS Agreement reads:

[88] At least Canada does not seem to contest that these are provisional measures, see Canada's First Submission para 379

[89] EC first written submission para 589

> In cases where relevant scientific evidence is insufficient, a Member may provisionally adopt sanitary or phytosanitary measures on the basis of available pertinent information, including that from the relevant international organisations as well as from sanitary or phytosanitary measures applied by other Members. In such circumstances, Members shall seek to obtain the additional information necessary for a more objective assessment of risk and review the sanitary or phytosanitary measure accordingly within a reasonable period of time. (Emphasis added)

136. According to Article 5.7 a member may provisionally adopt measures "where relevant scientific evidence is insufficient." This can be done "on the basis of available pertinent information".

137. Assessments made under Article 5.7 do not generally need to contain the same comprehensive set of elements normally included in risk assessments under *inter alia* Article 2.2 or Article 5.1. This seems clear from the wording of the last sentence of Article 5.7, which provides for "a more objective assessment of risk" to be made "within a reasonable period of time". Implicitly, this means that something less than a complete assessment of risk may provisionally suffice. It also follows from Article 2.2, that a measure taken pursuant to Article 5.7 may be maintained "without sufficient scientific evidence". Thus, provisional measures may be enacted without having undertaken a complete and conclusive risk assessment.

138. In *Japan – Apples* the Appellate Body endorsed the Panel's view that *"under [the Panel's] approach, Article 5.7 would be applicable to a situation where a lot of scientific research has been carried out on a particular issue without yielding reliable evidence"*.[90]

139. The facts referred to by the Appellate Body in *Japan – Apples*[91] related to a situation where "*scientific studies as well as practical experiences have accumulated for the past*

[90] See Appellate Body Report, *Japan – Apples* at para. 185
[91] See Panel Report *Japan – Apples* at para 8.219

200 years. The Panel's remark was that this *"is clearly not the type of situation Article 5.7 was intended to address".* [92]

140. The situation in the present case is noticeably different from that of *Japan – Apples*. Biotechnology is still in its infancy. Much of the scientific findings are inconclusive or ambiguous. Scientists often do not agree on the significance of certain findings. Since these are very complex matters, it may take several years before one may find reliable evidence which allows one to conclude prudently as to the consequences to health and/or environment as regards the GMOs at issue in the present dispute. The potential downside would be considerable if the GMOs at issue should indeed turn out to have harmful effects, but are allowed to be commercialised.

141. The situation which characterises the present dispute is therefore one where "a lot of scientific research has been carried out on a particular issue without yielding reliable evidence".

142. In this context the Panel in *Japan – Apples* also noted that *"Moreover, this is evidence in which the experts have expressed strong and increasing confidence."*[93] This is not the situation in the present dispute, where, much of the newer scientific findings cast doubts as to safety of certain GMOs, particularly the use of antibiotic resistance genes as marker genes.

143. The facts in this dispute do not allow for an in-depth analysis of what type of information that formed the basis for individual Member States' risk assessments. For the Panel it should suffice, however, to note that much relevant scientific material of a general nature was available at the time of Member State national measures, as shown above in Chapter 2. This general knowledge was sufficient in order to bring these assessments into the ambit of the SPS Agreement Article 5.7.

144. We note that the Appellate Body in *EC – Hormones* states that a "SPS measure might well find its objective justification in a risk assessment carried out by another Member".[94]

[92] Ibid
[93] Ibid
[94] See Appellate Body Report WTO/DS26/AB/R and WTO/DS48/AB/R, *EC– Hormones* at para. 190

Even though this statement was made in relation to SPS Agreement Article 5.1, the same reasoning should be equally applicable in relation to other WTO Member's assessments under Article 5.7.

145. Firstly, Norway holds that information that may be collected from open sources, is "available pertinent information", on which basis any WTO member "may provisionally adopt sanitary or phytosanitary measures".

146. Secondly, when members of a customs union, like the EC, make assessments based on "available pertinent information", other members of the customs union are likely to have relied on such information, when making their own decisions. In this context it should be noted that an EC Member State is explicitly required under Article 16 of Directive 90/220/EC to share all information on which a national measure is based.[95].

147. Thirdly, such sharing of information is also a requirement under the EEA Agreement.[96] It means that when Norway under its Gene Technology Act prohibits a GMO which has already been approved by the EC Commission, Norway must share that information with the EC and its Member States.[97]

148. On the whole, there exists a presumption that the requisite available pertinent information was at hand in order for the EC Member States to both identify the risks posed by these GMOs as well as to draw the conclusion that a provisional national measure is in conformity with the SPS Agreement Article 5.7.

149. Under Article 5.7 "Members shall seek to obtain the additional information necessary for a more objective assessment of risk and review the sanitary or phytosanitary measure accordingly within a reasonable period of time."

[95] The last sentence of Article 16 point 1 reads:" It [the Member State] shall immediately inform the Commission and the other Member States of such action and give reasons for its decision" (Exhibit US-25).
[96] See the last sentence of point (b) 1 in the adaptation of the EEA Agreement to Article 16 of Directive 90/220/EC which reads "It shall immediately inform the other Contracting Parties through the EEA Joint Committee of such action and give reasons for its decision". (Exhibit NOR-109)
[97] See letter from Ministry of Environment of 9.October 1997 to the European Commission on the ban of 1. October 1997 (Exhibit NOR-108). See also letter from the Norwegian Mission of 15. December 2000 to the European Commission on the ban of 15. December 2000 (Exhibit NOR-19).

150. Much research is continuously being done world-wide in order to obtain better insight into these complex issues. Specialised agencies are established in order to allow regulatory authorities a better and more systematic access to scientific evidence. The establishment of the European Food Safety Authority (EFSA) will contribute to improving regulatory authorities' scientific basis for the EC risk management. At the same time a better and more comprehensive legal framework is being set up, like under the recent EC legislation. The EC has also set up a Working Group to consider the implementation of Article 4 (2) of Directive 2001/18/EC, as mentioned above in Chapter 2.4.3.2. This is clearly a situation different from that of *Japan-Apples*.

3.3.1 Interpretation of SPS Article 5.7 in the light of Articles 10(6) and 11(8) of the Cartagena Protocol on Biosafety

151. As stated by the EC, the Cartagena Protocol places considerable emphasis on the precautionary principle[98]. The principle is specified in Articles 10(6) and 11(8) of the Protocol.

152. Article 10(6) states:

> "[l]ack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects of a living modified organism on the conservation and sustainable use of biological diversity in the Party of import, taking also into account risks to human health, shall not prevent that Party from taking a decision, as appropriate, with regard to the import of the living modified organism in question [-] in order to avoid or minimise such potential adverse effects."

153. As has been demonstrated in Chapter 2.2 and 2.4 above, there was, and still is lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects of the living modified organisms prohibited in certain EC Member States and Norway. Even though not all parties to the present dispute are parties to the Cartagena Protocol on Biosafety, 103 states are signatories to it. Thus the Protocol forms part of generally recognised international law and is as such, an important interpretative instrument in relation to parts of the SPS Agreement.

[98] EC first written submission paras 105-108

3.3.2 Conclusion

154. The requirements under SPS Article 5.7 are met in relation to the three GMOs

3.4 The TBT Agreement is not applicable to measures against antibiotic resistance marker genes.

155. Canada and Argentina argue that to the extent that the SPS Agreement is not applicable, the Member State national measures could be reviewed under various subparagraphs of Article 2 to the TBT agreement[99].

156. Article 2 of the TBT Agreement reads in parts:

> Article 2
>
> Preparation, Adoption and Application of Technical Regulations by Central Government Bodies
>
> With respect to their central government bodies:
>
> 2.1 Members shall ensure that in respect of technical regulations, products imported from the territory of any Member shall be accorded treatment no less favourable than that accorded to like products of national origin and to like products originating in any other country.
>
> 2.2 Members shall ensure that technical regulations are not prepared, adopted or applied with a view to or with the effect of creating unnecessary obstacles to international trade. For this purpose, technical regulations shall not be more trade-restrictive than necessary to fulfil a legitimate objective, taking account of the risks non-fulfilment would create. Such legitimate objectives are, *inter alia:* national security requirements; the prevention of deceptive practices; protection of human health or safety, animal or plant life or health, or the environment. In assessing such risks, relevant elements of consideration are, *inter alia:* available scientific and technical information, related processing technology or intended end-uses of products.

157. In Norway's view the arguments of Canada and Argentina do not correctly reflect the content of Article 2.2 The reason being that EC Member State national measures are not "technical regulations" within the meaning of the TBT Agreement.[100] They do not contain general descriptions of a normative nature applicable to an undetermined number of producers. In the case in *EC – Asbestos*, the Appellate Body *inter alia* held that since the national measure "lays down "characteristics" for all products that might contain

[99] Canada first written submission paras 473-505 and Argentina first written submission paras. 547-592.
[100] EC first written submission para 642

asbestos"[101] (underlining added), the measure was covered by the TBT Agreement Article 2.2 In our dispute, however, the national measures do not apply to all GMOs or even all GMOs coding for antibiotic resistance. Rather, the measures contain a single ban of one particular GMO. Moreover, this ban is addressed to one specific manufacturer or right holder. The measure creates legal rights and obligations only upon this addressee.

158. In this respect, how the measure is designated under national law is not decisive for whether Article 2.2 will be applicable or not ("Decree", "Notice", "Ministerial decision" etc). Since the national measures are individual decisions directed towards an individual manufacturer or right holder and not normative acts of general application, they fall outside the scope of Article 2 of the TBT Agreement.

3.4.1 Conclusion

159. The TBT Agreement is not applicable in relation to the three GMOs.

3.5 The GATT 1994

3.5.1 The relevant measures are not in breach of Article III: 4.

Article III:4 reads in relevant part:

> The products of the territory of any contracting party imported into the territory of any other contracting party shall be accorded treatment no less favourable than that accorded to like products of national origin in respect of all laws, regulations and requirements affecting their internal sale, offering for sale, purchase, transportation, distribution or use. The provisions of this paragraph shall not prevent the application of differential internal transportation charges which are based exclusively on the economic operation of the means of transport and not on the nationality of the product.

160. Canada and Argentina claim that [some] of the Member State national measures violate Article III:4 of GATT 1994. [102]These allegations are unfounded.

161. In order for a violation of Article III:4 to occur, several conditions will have to be fulfilled. A main requirement is that imported products are treated less favourably than

[101] Appellate Body in *EC- Asbestos* WT/DS135/AB/R para 75

[102] Canada first written submission para 444. Argentina first written submission paras 524 – 526

domestic products. In this dispute, the national origin of the manufacturers are not a relevant issue. As shown throughout this submission, quite different concerns have led to these national measures. Indeed, most of the GMOs subject to Member State national measures have in fact been notified by companies incorporated in the EC and belong to such companies.[103] Thus, the national measures do not distinguish on the basis of nationality and there is no evidence that the national measures are in particular addressed at the imported GMOs. This is also the case with the Greek national measure, which according to its intended legal effects applies *erga omnes*.

162. Moreover, in order to be caught by Article III:4 of GATT 1994, the Complainants must show that these GMOs are "like" products. Several factors will contribute to deciding whether these are "like" products or not. Norway will merely point to the fact, as demonstrated in Chapters 2.3, that most WTO members distinguish between GMOs and its conventional counterparts as regards regulatory regimes. This is because GMOs in fact may have different effects on health and environment than their conventional counterparts. Also, as shown in Chapters 2.4.2.2 and 2.4.3.2, international organisations are increasingly viewing products containing GMOs with genes coding for antibiotic resistance as distinct from conventional products. Also, the growing demands for labelling of GMOs, which come as a response to consumer demands, indicate that GMOs should not be treated as "like" products.

163. In conclusion, the Member State measures in relation to the three GMOs are not in breach of GATT 1994 Article III:4.

3.5.2 GATT 1994 and measures against antibiotic resistance marker genes in relation to Article XX

164. Article XX reads in relevants parts:

> General Exceptions
>
> Subject to the requirement that such measures are not applied in a manner which would constitute a means of arbitrary or unjustifiable discrimination between countries where the same conditions prevail, or a disguised restriction on international trade, nothing in this Agreement shall be construed to prevent the adoption or enforcement by any contracting party of measures:

[103] See EC first written submission paras 632-633

(*b*) necessary to protect human, animal or plant life or health;
.....

(*g*) relating to the conservation of exhaustible natural resources if such measures are made effective in conjunction with restrictions on domestic production or consumption;

165. Even if other articles of the GATT 1994 were breached, Article XX, in particular sub-paragraph (b) provides a defence with respect to the three GMOs discussed here. As shown in the three Norwegian risk assessments referred to in Chapter 2.4, risks to human and animal health may be invoked in relation to these GMOs. The Appellate Body has in relation to Article XX (g) stated the following on its interpretation in relation to concerns not present at the time of the drafting: [*The words] must be read by a treaty interpreter in the light of contemporary concerns of the community of nations about the protection and conservation of the environment.*[104]" The same must apply in relation to concerns rising from new technologies.

3.5.3 Conclusion

166. The Member State measures in relation to the three GMOs are justified under GATT 1994 Article XX.

4. CONCLUDING REMARKS

167. Norway respectfully requests the Panel to take the facts and arguments presented above into consideration when making its findings and recommendations.

[104] Appellate Body in *US – Certain Shrimp products* WT/DS58/AB/R at para 129