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

**(WT/DS/291, 292, and 293)**

**Amicus Curiae Brief**

**June 1st, 2004**

**Center for International Environmental Law (CIEL)**
**Friends of the Earth – United States (FOE – US)**
**Defenders of Wildlife**
**Institute for Agriculture and Trade Policy (IATP)**
**Organic Consumers Association – United States (OCA – USA)**

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## I. Introduction

1. Amicus curiae briefs are fundamental in developing balanced and high-quality decisions in the World Trade Organization (WTO) dispute settlement system. A Panel is entrusted with conducting an "objective assessment" of the case before it, but as the multilateral trade framework continues to expand and increase its areas of influence, carrying out such an assessment becomes more challenging.[1] Since Panels are not forced to restrict their analysis to the arguments presented by the parties to the dispute, however, relevant information and technical advice put forth by non-parties – in the form of amicus curiae briefs – can prove valuable in achieving just and well-rounded decisions.[2] Moreover, through the consideration of amicus curiae briefs, Panels can ensure the participation of all affected sectors of the public, which, particularly in cases of high political sensitivity, also increases the legitimacy of decisions made in the context of the WTO dispute settlement.[3]

2. The present amicus curiae brief aims to contribute in such an important manner in the case of European Communities – Measures Affecting the Approval and Marketing of Biotech Products (*EC-Biotech*).[4] By providing information that will allow the Panel to consider the full range of available scientific evidence, as well as expertise in the relevant legal regimes, the present brief seeks to constitute an instrument for a balanced and high-quality decision. In this regard, the undersigned *amici* are well respected in the environmental community and recognized in that context for their expertise in the field of trade and environment, and will thus provide valuable factual and technical information for the Panel's consideration.

3. In particular, the present amicus curiae brief aims to provide factual and technical information to assist the Panel in the interpretation of the term "insufficient scientific evidence" under Article 5.7 of the Agreement on Sanitary and Phytosanitary Measures (SPS Agreement).[5] While "scientific uncertainty" is not the same as "insufficient scientific evidence," WTO jurisprudence is not clear as to the influence of uncertainty in determining whether the scientific evidence is insufficient in a given situation.[6] Since substantial uncertainty remains as to the effects of genetically modified organisms

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[1] Understanding on Rules and Procedures Governing the Settlement of Disputes (DSU), April 15, 1994, Marrakech Agreement establishing the World Trade Organization, Annex 2 (1994), *at* article 11.

[2] EC – Measures concerning Meat and Meat Products (EC-Hormones), WT/DS26/AB/R, WT/DS48/AB/R (January 16, 1998), *at* para. 156.

[3] Nevertheless, the role of amicus curiae briefs is still severely limited by the lack of clear procedures, as well as by the difficulties faced by non-parties in acquiring relevant information about the case. In the present case, for instance, only the United States and Canada made their first submissions public before the first Panel hearing.

[4] European Communities – Measures Affecting the Approval and Marketing of Biotech Products (EC-Biotech) (WT/DS/291, 292, and 293).

[5] WTO Agreement on the Application of Sanitary and Phitosanitary Measures (SPS Agreement), *available at* http://www.wto.org/english/docs_e/legal_e/15sps_01_e.htm.

[6] Japan – Measures Affecting Imports of Apples (Japan – Apples), WTO Docs. WT/DS245/AB/R, (November 26, 2003), at para. 184.

(GMOs) on human, animal, and plant life and health, it is an issue of significance in the *EC-Biotech* case and of considerable interest to the undersigned *amici.*

4. Consequently, Section II of the present amicus curiae brief will describe the scientific uncertainties remaining in the context of GMOs. Section III will begin by analyzing how the text and objective of the SPS Agreement command interpreting "insufficient scientific evidence" to be essentially influenced by the existence of scientific uncertainty. Then, Section III will examine how relevant rules and principles of international law, in an eventual finding of lack of clarity in the provisions of the SPS Agreement, also support such a conclusion. Finally, Section IV will conclude by summarizing the arguments of the present amicus curiae brief.

## II. Statement of facts: Evaluating the human, animal, and plant health impacts of GMOs entails substantial scientific uncertainty

### A. Background

5. Genetic modification, the process through which an organism is modified by the application of recombinant DNA (rDNA) technology,[7] can involve either the transfer of genes from one (or more) species to another or the manipulation of genetic material within a species.[8] In either case, genetic modification inevitably involves significant scientific uncertainty that is relevant to regulators, consumers, and citizens more generally.[9]

6. This scientific uncertainty has both technological and evidentiary bases. Technologically based scientific uncertainty stems from factors that include, but are not limited to, the inherent imprecision of currently employed rDNA techniques; the use of powerful, often viral, promoter sequences in genetic constructs; and the generation in GMOs of novel proteins to which humans and animals have never before been exposed. Scientific uncertainty also results from the still-considerable ignorance of the composition and functioning of organismal genomes that are subject to genetic manipulation, and serious inadequacies in studies conducted to assess the potential health

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[7] Committee on Biological Confinement of Genetically Engineered Organisms, National Research Council of the National Academies, Biological Confinement of Genetically Engineered Organisms 15 (The National Academies Press 2004).

[8] Nam et al., "Accelerated growth, gigantism and likely sterility in autotransgenic triploid mud loach *Misgurnus mizolepis*" 32(4) Journal of the World Aquaculture Society 353 (2001); Nam et al., "Dramatically accelerated growth and extraordinary gigantism of transgenic mud loach *Misgurnus mizolepis"*, 10 Transgenic Research 353 (2001).

[9] The first U.S. submission to the *EC-Biotech* case, however, denies the existence of potential hazards from GMOs. At paragraph 27, the U.S. brief states:

> The safety of biotech products has been confirmed by scientific reports issued under the auspices of renowned international institutions, such as the FAO and WHO, seven national and international academies of science, the Organization for Economic Cop-operation and Development, as well as independent scientists in the United States, Africa, and Europe. (footnotes omitted)

This sweeping statement and the accompanying text mischaracterize the wide range of scientific opinion on the health and environment risks posed by the diverse products of commercial and genetic modification and ignore the scientific uncertainty inherent in evaluating such risks

and environmental impacts of GMOs. Together, these factors give rise to substantial scientific uncertainty concerning the hazards posed by GMOs to human health and the environment. The grounds for scientific uncertainty are discussed in detail below.

**B. Evidentiary grounds of substantial scientific uncertainty**

9. Addressing the evidentiary grounds of scientific uncertainty in the field of genetic modification entails correcting some common misconceptions concerning the scientific method and the scientific review process as it relates particularly to biotech products. At the outset, it is important to understand that any blanket assertion on the safety of a class of products as broad as the products of rDNA technology is *ipso facto* unscientific in nature, just as unscientific, in fact, as a blanket assertion that all biotech products are hazardous would be. A scientist can reach conclusions regarding the safety or risks of a particular product only if he or she is familiar with the often substantial scientific literature concerning it and finds that literature adequate to form a well-founded opinion. This "case-by-case" assessment approach is the hallmark of sound scientific procedure in any discipline. It is absolutely essential in the arena of biotechnology, because biotech products are the result of random, haphazard, and unrepeatable gene insertion processes that routinely cause unpredictable, unintended effects (see part C, below). It is not surprising, therefore, that the need to evaluate the risks of GMOs on a case-by-case basis has been widely recognized.

10. In this regard, the scientific reports cited in the U.S. brief frequently contain internal contradictions, at least in terms of their implications. For instance, these reports combine weak statements to the effect that there is "no evidence of harm" from biotech products with extensive criticism of the deficiencies in the biotech product testing procedures upon which such claims are made. Another problem with the "no evidence of harm" statement used in many reports is that it applies equally to a biotech product on which little or no testing has been conducted (absence of evidence) and a biotech product that has come up negative for adverse effects after extensive testing (evidence of absence). An expert committee of the U.S. National Academy of Sciences explicitly criticizes the unscientific use of this statement by the U.S. Department of Agriculture (USDA) to imply environmental safety (i.e., implying evidence of absence), when in fact there is not sufficient evidence on which to base a meaningful evaluation due to lack of environmental monitoring:

> "Similarly, claims concerning the lack of effects from the tens of millions of hectares of transgenic crops that have been planted in the United States during the past three years are nonscientific. There has been no environmental monitoring of these transgenic crops, so any effects that might have occurred could not have been detected. The absence of evidence of an effect is not evidence of absence of an effect."[10]

11. "No evidence" claims are even more frequently misused to illegitimately dismiss concerns about the human risks of GMOs. Numerous expert review panels and scientists

[10] National Research Council, Environmental Effects of Transgenic Plants (2002), p. 79

have recommended the use, or consideration of the use, of post-marketing surveillance to detect any human health impacts of genetically modified foods in the population at large, in analogy to the procedure employed when first marketing a drug.[11] The need for post-marketing surveillance is even more acute given the subjective, undefined nature of pre-market testing regimens. To our knowledge, however, such post-marketing surveillance has never been carried out for a genetically modified food, which means that any health impacts that may have occurred in the 10-year history of commercial genetically modified food production and consumption have gone unrecorded. Given this complete failure to collect data that are regarded as essential by many experts in the field, one must conclude that "no evidence" claims with respect to the human health impacts of GMOs have very little value.

12. Even when evidence exists, it is often not available for independent review due to intellectual property considerations. Two of the least-known facts in the world of biotechnology are that:

(1) The great majority of pre-market studies that form the basis of assessments of GMOs for potential human health or environmental impacts are *not* peer-reviewed literature authored by independent scientists or government regulators, but rather are unpublished, non-peer-reviewed studies conducted by the GMO developer or its contractor. One of many examples is the EPA's 2001 human health assessment of pesticide-producing Bt crops, which cites 22 unpublished corporate studies, with initially only 1 ancillary literature citation.[12]
(2) Access by independent scientists and the public to some or most of these unpublished studies is denied or restricted as "confidential business information" (CBI) of the developer. An expert committee of the National Academy of Sciences, for instance, found it impossible to fulfill its charge of reviewing the regulatory performance of the USDA's Animal and Plant Health Inspection Service [APHIS] with respect to GM crops due to excessive CBI claims.[13]

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[11] *See*: "Evaluation of Allergenicity of Genetically Modified Foods," Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, January 22-25, 2001, p. 9; Workshop on "Genetically modified foods and allergenicity: safety aspects and consumer information," Consumer & Biotechnology Foundation with the European Federation of Asthma and Allergy Associations, May 28-29, 1999, section 5.2; "Sets of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Session II – Mammalian Toxicity Assessment Guidelines for Protein Plant Pesticides," FIFRA Scientific Advisory Panel Report No. 2000-03B, September 28, 2000, p. 11; Wal, J. M. "Strategies for Assessment and Identification of Allergenicity in (Novel) Foods," International Dairy Journal 8 (1998), pp. 413-23.

[12] Biopesticides Registration Action Document (BRAD), "*Bacillus thuringiensis* Plant-Incorporated Protectants: Product Characterization & Human Health Assessment," US EPA, October 15, 2001, *available at* www.epa.gov/pesticides/biopesticides/pips/bt_brad2/2-id_health.pdf.

[13] National Research Council, Environmental Effects of Transgenic Plants (2002), p. 177. The expert stated: "Many people, including those generally supportive of biotechnology, decry the apparently large amount of data and information in [biotech company] submissions [to the USDA] marked 'CBI' (confidential business information). Under this CBI stamp, *all manner of data are hidden from public view and even from independent scientific scrutiny.* … This committee sometimes found that it could not provide an independent scientific assessment of rulings because of the broad use of CBI. … APHIS appears to accept without question an applicant's assertion of what is CBI. Public credibility is eroded when the same

13. Even national governments and their regulatory agencies are sometimes denied critical information needed to make informed regulatory decisions. One recent example is the refusal of the Monsanto Corporation to hand over to the German government a study on a rat feeding trial with its MON863 pesticide-producing Bt corn that indicated abnormalities in the development of blood cells and potential kidney damage on the grounds that the study was CBI.[14] Similarly, biotechnology companies have failed to comply with U.S. Food and Drug Administration (FDA) requests for data on GM crops under FDA review on at least three separate occasions.[15]

14. For this and other reasons, regulatory agencies often base their assessments on incomplete data. As a result, reviews by national regulatory agencies are not adequate to support any claim regarding the safety of GMOs. The FDA, for example, does not review original corporate studies on genetically modified crops. Instead, the agency requests submission of only a packet of "summary data" with the results and conclusions of whatever studies the genetically modified crop developer has chosen to conduct, but excluding crucial methodological data (i.e., how tests were conducted) absolutely required for a critical review. Moreover, the FDA's review process is voluntary, not mandatory, so a genetically modified crop developer is not required to submit any data to the agency at all. At the end of the voluntary consultation process, the FDA merely issues a note conveying the company's conclusion that its genetically modified crop is "substantially equivalent" to conventional varieties; that is, the FDA does *not* approve any genetically modified crop as safe.[16] Despite these facts, one often encounters the claim that FDA has "approved" certain GM crops as safe.

15. Finally, it is also commonplace to encounter statements that genetic modification and GMOs do not entail any new categories of risks, i.e., any types of risks that are not raised by traditional means of breeding or otherwise developing new varieties of organisms.[17] From a regulatory perspective, such statements are inconsistent with the reality posed by the extraordinary speed at which genetic modification allows radical

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information marked CBI in APHIS documents is not considered CBI and is open to public inspection in other jurisdictions, such as Canada or Europe." (emphasis added)

[14] Greenpeace press release, "Monsanto defies German government on risk study as EU Commission prepares to approve GM maize", May 18, 2004.

[15] Gurian-Sherman, D. (2003), "Holes in the Biotech Safety Net: FDA Policy Does Not Assure the Safety of Genetically Engineered Foods", Center for Science in the Public Interest, January 2003, *available at* www.cspinet.org/new/pdf/fda_report__final.pdf.

[16] The letter sent by the FDA to Monsanto upon completion of the consultation process for Monsanto's Bt corn (events MON809 and MON810) is typical. It reads in part: "Based on the safety and nutritional assessment you have conducted, it is our understanding that *Monsanto has concluded* that corn products derived from this new variety are not materially different in composition, safety, and other relevant parameters from corn currently on the market, and that the genetically modified corn does not raise issues that would require premarket review or approval by FDA. … as you are aware, it is *Monsanto's responsibility* to ensure that foods marketed by the firm are safe, wholesome and in compliance with all applicable legal and regulatory requirements" (our emphasis). See Letter for BNF No. 34, dated Sept. 25, 1996, *available at* www.cfsan.fda.gov/~lrd/biocon.html.

[17] *See, e.g.,* National Research Council, Environmental Effects of Transgenic Plants 5 (National Academies Press 2002) (regarding plants); Note 33 of the United States' submission.

changes to be made in organisms (including in microorganisms such as viruses and bacteria as well as in fungi, algae, plants, and insects, fish and other animals), which raises new risks in terms of: the ability of ecosystems to adapt gradually; the ability to anticipate environmental and health effects; and the ability to adapt--or develop new--regulatory regimes to effectively, efficiently and credibly manage the risks associated with particular GMOs.

16. In addition, the comparison between rDNA techniques and traditional breeding practices is fundamentally flawed. Traditional breeding practices, nearly all of which are extensions of natural reproductive processes, have histories of safe use dating back, in many cases, thousands of years. In contrast, the commercial use of rDNA techniques for human use began only 22 years ago, when genetically modified bacteria-produced insulin was first introduced to the market; genetically modified plants have been commercially available for only a decade. Not only is one to two decades too short a period of time to constitute a "history of safe use" for a radical new drug or crop production method, there is compelling positive evidence of human health and environmental impacts from certain GMOs (see Sections C, D, and E, below).

17. Consequently, it is absolutely clear that GMOs and their use do entail substantial uncertainty. Three types of uncertainty regarding GMOs are discussed below: (1) Unintended effects of genetic modification arising from: the random nature of rDNA techniques; the use of powerful, often viral, promoter sequences to drive expression of the transgene; and our still considerable ignorance of organismal genomes and their cellular interactions; (2) Uncertainty regarding the effects of exposing humans, animals and other living organisms to the novel proteins generated by many GMOs; and (3) Unintended environmental impacts. The discussion below is phrased in terms of genetic modification involving the transfer of genetic material between species, but it also applies to genetic modification within one species.

## C. The unintended effects of genetic modification arising from the random nature of rDNA techniques, the use of powerful promoter sequences to drive expression of the transgene, and the ignorance of organismal genomes and their cellular interactions

18. Genetic modification as defined here means the introduction of foreign genes (i.e., transgenes) into organisms via rDNA techniques. The most common rDNA techniques currently employed in the genetic modification of plants are particle bombardment via "gene gun," Agrobacterium-mediated transformation and electroporation. These techniques do *not* permit control or determination of the sequence of the transgene(s) that is inserted, the site of transgene insertion in the host genome, or the number of copies of the transgene that are integrated. In addition, these techniques are often accompanied by fragmentation of the transgene[18] and/or disruption of host organism genes or regulatory

[18] On transgene fragmentation, *see*: Freese, B. "Genetically Engineered Crop Health Impacts Evaluation," Friends of the Earth, July 2003, www.foe.org/camps/comm/safefood/gefood/index.html; on disruption of native DNA flanking transgene insertion sites, see: Windels et al (2001). "Characterization of the Roundup Ready soybean insert," European Food Research Technology, Abstract Volume 213 (2), pp. 107-112.

DNA. As a result, genetic modification is routinely accompanied by unpredictable and unintended effects including cell death, overproduction of native allergens or toxins, nutritional deficits, and creation of novel fusion proteins (i.e., proteins from inadvertent combination of host and foreign DNA in the transformation process) with unknown properties.[19]

19. Random and unpredictable genetic modification techniques thus lack a cardinal feature of both scientific method and reliable commercial technologies – repeatability. That is, one never achieves the same result by performing the "same" genetic modification experiment due to the inherent imprecision and unpredictability of rDNA techniques. Each and every product of plant genetic modification is in fact formally known as an "event" to emphasize its unique nature. Such concerns were raised, for instance, in the drafting of FDA regulations for genetically modified plants, but ultimately not addressed by these regulations.[20]

20. Transgenes are not introduced alone, but rather only as parts of complex "genetic constructs" or "transformation vectors" that incorporate numerous other DNA segments from various organisms and of various function. These regulatory DNA segments include promoters, enhancers, origins of replication and termination sequences. Promoters, which are often of viral origin, instruct the host cell to generate the desired protein from the transgene. Constitutive promoters, such as the 35S cauliflower mosaic virus promoter sequence, drive production of the foreign protein in every tissue of the plant, creating numerous opportunities for the novel protein to cause potentially hazardous unintended effects through disruption of various cellular processes. Another hazard of promoters is their potential to inadvertently cause overproduction of native proteins, or to activate dormant (i.e. cryptic) genes, also thereby disrupting cellular metabolism.[21]

21. Even though scientists recently sequenced (i.e., determined the composition of) the total genetic material (i.e., genome) of humans and mice, scientists are still ignorant of the function of most of the DNA of these genomes. Scientists have even less knowledge of plant genomes; of the major crop plants, only the rice genome has been

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[19] For listings of a few of the many unintended effects in the world of plant genetic modification, *see*: Kuiper, H.A.., Kleter, G.A., Noteborn, H..P,J.M., Kok, E.J. (2001). "Assessment of the food safety issues related to genetically modified foods". *The Plant Journal* **27**(6), 503-528; and Haslberger, A.G. (2003). "Codex guidelines for GM foods include the analysis of unintended effects". *Nature Biotechnology* **21**(7) , 739-741.

[20] "Comments on Biotechnology Draft Document, 2/27/92." Draft memo from Dr. Louis J. Pribyl (recipient not cited), 3/6/92. http://www.bio-integrity.org/FDAdocs/04/04.pdf. FDA scientist Dr. Louis J. Pribyl raised these concerns about unintended (a.k.a. pleiotropic) effects in a 1991 memo commenting on FDA's draft regulations for genetically modified plants: "When the introduction of genes into plant's genome randomly occurs, as is the case with the current technology (but not traditional breeding), it seems apparent that many pleiotropic effects will occur." [sic] Dr. Pribyl's concerns were not addressed in FDA's final regulations.

[21] *See, e.g., supra* note 24, for concerns raised by FDA's Dr. Pribyl about "new, powerful regulatory elements being randomly inserted into the genome" that could cause "cryptic pathway activation" that breeders might miss .

fully sequenced. Scientists are discovering that much of what is commonly known as "junk DNA" because it does not code for proteins has important regulatory functions, such as encoding "active RNA" responsible for modulating expression of proteins from genes, or protecting the cell from viruses through gene silencing mechanisms.[22] As the many functions of "junk DNA" are elucidated, it is becoming clear that integration of transgenes into these larger regions could also have potentially hazardous unintended effects through disruption of cellular regulatory functions. This explains why European scientists are advocating more sophisticated, non-targeted techniques such as metabolic profiling for the detection of the unintended effects of genetic modification in plants.[23]

### D. Uncertainty regarding the effe cts of exposing humans, animals and other living organisms to the novel proteins generated by many GMOs

22. Most GMOs generate novel proteins to which humans, animals and other living organisms have never been exposed. While it was once thought that biopharmaceuticals, such as insulin, produced through genetic modification of bacteria and animal cell cultures with artificial "human" genes would be effectively identical to their native human counterparts, scientists have discovered that some biotech "human" drugs can cause auto-immune disorders for reasons that remain unclear. Two examples include genetically engineered versions of megakaryocyte growth and development factor (MGDF), which was found to induce internal bleeding in clinical trial patients, and Eprex (a biotech version of the body's natural erythropoietin), which is used to treat anemia and has been implicated in up to 160 cases of red cell aplasia, or virtual shutdown of the body's red blood cell production.[24] Most important from our perspective is that these immune system responses have taken scientists and regulators alike by surprise.[25]

23. Other potential effects of genetic modification have concerned scientists for longer. For example, the long-standing concern that novel proteins produced by most genetically modified plants could cause allergic reactions has driven development of "decision-tree" protocols for testing novel, genetically modifed plant-produced proteins for potential allergenicity.[26] One class of genetically modified crops of particular concern in this regard is the pesticide-producing Bt crops, which generate novel versions of insecticides derived from the soil bacterium *Bacillus thuringiensis* (Bt). However,

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[22] *See, e.g.*, Contans, A. (2002). "Small Worms, Small RNAs, Big Questions," The Scientist, Vol. 16 (15), 7/22/02.

[23] Kuiper et al (2001). Assessment of the food safety issues related to genetically modified foods. *The Plant Journal* **27**(6), 503-528

[24] Tagliabue, J. "Mystery effect in biotech drug puts its maker on the defensive," New York Times, Oct. 2002.

[25] See, e.g., Aoki, N, "Protein therapies spark scrutiny: researchers weigh potential risk of immune responses," The Boston Globe, Nov. 27, 2002, quoting Dr. Burt Adelman of the biotech firm Biogen found the reactions to MGDF "stunning:" "The conventional wisdom had been that this was a theoretical risk … nobody saw it coming. If you're in my business, it's really unnerving."

[26] For example, *see*: "Evaluation of Allergenicity of Genetically Modified Foods," Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, Jan. 22-25, 2001, *available at* www.fao.org/es/ESN/food/pdf/allergygm.pdf.

despite suggestive evidence indicating that Bt protein may cause allergies,[27] neither Bt crops nor other genetically modified crops have been adequately tested for allergenicity due to faulty testing by genetically modified crop developers and the failure of regulatory agencies to establish test protocols. In fact, the U.S. Environmental Protection Agency (EPA) ignored evidence that the insecticidal protein found in the mostly widely planted Bt crops (Cry1Ab) has three characteristics of allergenic proteins: digestive stability, heat stability and structural similarity to a known food allergen (vitellogenin, an egg yolk allergen). The latter finding, surprisingly, was ignored by the EPA despite the fact that it was made by a scientist at the EPA's sister agency, the FDA.[28]

24. Novel substances produced by GMOs may also be responsible for toxic effects. For instance, there is strong evidence that genetic modification was at fault for dozens of deaths and several thousand injuries from a condition known as eosinophilia myalgia syndrome in individuals who consumed a version of the amino acid tryptophan produced by the Japanese company Showa-Denko using genetically modified bacteria. The leading hypothesis for the cause of these deaths and injuries is that the increased concentrations of tryptophan resulting from the use of genetically modified bacteria to increase production over that achieved with unmodified bacteria fostered the accidental formation of a toxic compound composed essentially of two tryptophan molecules.[29]

25. The experimental use of genetically modified plants to produce pharmaceuticals and industrial compounds raises additional toxicological concerns, provoking criticism from the editors of the world's leading biotechnology journal.[30] While the identity of most of these "plant-made pharmaceuticals" (PMPs) and industrial compounds (ICs) is kept secret as confidential business information, we know that several PMPs and ICs have toxic properties. For instance, the protease inhibitor aprotinin, generated in genetically modified corn by the U.S. company ProdiGene, Inc., is known to cause pancreatic disease upon oral ingestion by test animals and also kill a broad range of insects exposed to it. Avidin, another corn-generated protein developed by ProdiGene that is already being marketed as a research chemical, is known to cause vitamin B deficiency in animals and humans upon oral ingestion, and also to kill a broad range of insects. A third PMP, trichosanthin, was generated in tobacco by means of genetically engineered viruses in 1991, 1996 and perhaps subsequent years. Trichosanthin, which was once considered a potential AIDS drug, is used traditionally in China to induce abortions, and has a number of serious toxic effects. None of these PMPs were

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[27] Bernstein, I.L., Bernstein, J.A., Miller, M., Tierzieva, S., Bernstein, D.I., Lummus, Z., Selgrade, M.K., Doerfler, D.L. and Seligy, V.L. (1999). "Immune responses in farm workers after exposure to *Bacillus thuringiensis* pesticides". *Environmental Health Perspectives* **107**(7), 575-582; *see also*: SAP Bt (2000). "Bt Plant-Pesticides Risk and Benefit Assessments". *FIFRA Scientific Advisory Panel*. SAP Report No. 2000-07, *available at* www.epa.gov/scipoly/sap/2000/october/octoberfinal.pdf.

[28] For a case study of the potential health impacts of Bt corn, *see*: Freese, B. "Genetically Engineered Crop Health Impacts Evaluation," Friends of the Earth, July 2003, *available at* www.foe.org/camps/comm/safefood/gefood/index.html.

[29] Raphals, P., "Does medical mystery threaten biotech?" Science, 249, 619, 1990; *see* also: Fagan, John, "Tryptophan Summary, Nov. 1997, *available at* www.psrast.org/jftrypt.htm.

[30] "Drugs in Crops: The Unpalatable Truth," *Nature Biotechnology*, February 2004, Vol. 22, Number 2, p. 133.

adequately reviewed for their human health or environmental risks before being "grown" out-of-doors by biotech companies under permit from the USDA.[31]

26. Currently employed genetically modified plant testing procedures do not evaluate these plants for potential toxic, carcinogenic, mutagenic, reproductive and other adverse effects. For instance, animal testing of genetically modified plants in the United States is limited to a 28-day rodent feeding trial for acute toxicity that employs a surrogate bacteria-generated version of the plant-produced genetically modified protein which may differ in important respects from the plant-produced GM protein to which consumers are actually exposed.[32] Longer-term feeding trials necessary to detect chronic and/or reproductive effects are generally not conducted. When companies do occasionally conduct longer-term animal feeding trials, the results are not reassuring. For instance, *La commission du genie biomoleculaire francaise* [CGB: the French Commission on Genetic Engineering] in the review of a 90-day subchronic toxicity rat feeding trial with a variety of Bt corn (event MON863) conducted by the Monsanto Corporation, noted a number of significant differences between the control group (fed conventional corn) and the rats fed MON863. Relative to the control group, males fed MON863 exhibited higher lyphocytes levels and more kidney anomalies; females exhibited reduced levels of reticulocytes (immature red blood cells) and significantly increased blood sugar levels.[33] As noted above, Monsanto has refused to turn over this study to the German government, which requested it for its own analysis after learning of the CGB's assessment.

### E. Uncertainty regarding the environmental impacts of GMOs

27. There are a variety of well known environmental risks associated with GMOs. The transfer of the widely employed herbicide-resistance trait, for instance, has resulted in the development of herbicide-resistant (HR) weeds.[34] HR weed also result from the increased use of herbicides with HR crops.[35] Due in part to HR crop-induced herbicide

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[31] Freese, B. (2002). "Manufacturing Drugs and Chemicals in Crops," Friends of the Earth, July 2002. www.foe.org/biopharm/

[32] Expert committees of the National Academy of Sciences and the Environmental Protection Agency have criticized this use of surrogate bacterial proteins in safety testing, yet the practice continues because biotech companies find it expensive to isolate adequate quantities of transgenic proteins from their crops. *See, e.g.*, "Genetically Modified Pest-Protected Plants: Science and Regulation," Committee on Genetically Modified Pest-Protected Plants, National Research Council, National Academy of Sciences, 2000, p. 65, *see*: http://books.nap.edu/catalog/9795.html. "Mammalian Toxicity Assessme1nt Guidelines for Protein Plant Pesticides," EPA's Scientific Advisory Panel, SAP Report No. 2000-03B, Sept. 28, 2000, p. 14, *available at* www.epa.gov/scipoly/sap/2000/june/finbtmamtox.pdf. For similar recommendations, and examples of immunologic differences between nearly identical proteins, *see*: "The StarLink Affair," Friends of the Earth, July 2001, sections 9.2 to 9.4, *available at* www.foe.org/safefood/starlink.pdf.

[33] Kempf, H. "L'expertise confidentielle sur un inquietant mais transgenique," Le Monde, 4/23/04, *available at* www.lemonde.fr/web/recherche_articleweb/1,13-0,36-362061,0.html.

[34] In Western Canada, scientists have discovered canola plants resistant to three different herbicides as a result of cross-pollination between various HR canola hybrids. The Royal Society of Canada considers this to be one of the most serious weed problems facing Canadian farmers.

[35] The most comprehensive survey to date, based on USDA data, suggests that use of HR crops has resulted in an increase in the use of herbicides of 70 million lbs. during the period of HR crop use, from 1996 to 2003. *See* Benbrook, C.M. (2003). "Impacts of Genetically Engineered Crops on Pesticide Use in the United States: The First Eight Years," BioTech InfoNet Technical Paper No. 6, Nov. 2003.

resistance in weed populations, farmers in Arkansas are projected to spend $9 million more dollars annually in weed control costs.[36] Weeds resistant to the herbicide most commonly used in association with HR crops, glyphosate (Roundup), for example, have been rapidly spreading in the United States.[37]

28. Another environmental concern with genetically modified crops is the potential for rapid build-up of insect resistance to the insecticidal proteins in Bt crops, which could render the related Bt insecticidal sprays used by organic farmers ineffective. The loss of this important tool could have disastrous implications for organic farmers as well as conventional farmers who use Bt sprays. In addition, contamination of conventional and organic crops with transgenic traits has made it increasingly difficult for conventional and organic farmers to "co-exist" with their genetically modified crop growing neighbors. Transgenic trait contamination occurs not only in conventional food and feed crops, but increasingly in conventional and organic seed crops as well. The contamination of conventional seed varieties with transgenic traits is particularly disturbing as seed crops are subject to extraordinary gene confinement protocols to maintain the purity of the particular variety. If even seed crops are becoming contaminated with transgenic traits, it becomes highly questionable whether co-existence schemes for genetically modified, conventional and organic crops are in fact feasible.[38]

29. Several reports by committees of the prestigious National Research Council of the U.S. National Academy of Sciences have concluded, however, that accurately predicting the environmental effects of GMOs is an uncertain proposition, at best. For example, the committee studying the environmental effects of genetically modified plants concluded:

> (1) small and large genetic changes [in non-transgenic organisms] have had substantial environmental consequences;
> . . .
> (4) introduction of biological novelty can have unintended and unpredicted effects on the recipient community and ecosystem;
> (5) *a priori* there is no strict dichotomy between the possibility of environmental hazard associated with releases of cultivated plants with novel traits and the introduction of nonindigenous plant species. [39]

30. A National Research Council report on animal biotechnology similarly stated:

> The committee considered environmental issues to be the greatest science-based concerns associated with animal biotechnology . . ., in large part due to the

[36] "Weed could cost farmers millions to fight," Associated Press, June 4, 2003. See www.weedscience.com for a thorough treatment of growing weed resistance to glyphosate and other herbicides.
[37] The most recent report of spreading glyphosate resistance among marestail weed populations in the U.S. state of Indiana. See Woodmansee, J. "Weed with Roundup immunity spreads across Indiana," Chronicle-Tribune, 5/26/04, *available at* www.chronicle-tribune.com/news/stories/20040526/localnews/503241.html.
[38] Mellon, M. & Rissler, J. (2004). "Gone to Seed: Transgenic Contaminants in the Traditional Seed Supply," Union of Concerned Scientists 2004. See: www.ucsusa.org.
[39] National Research Council, Environmental Effects of Transgenic Plants 4 (National Academies Press 2002).

> uncertainty inherent in identifying environmental problems early on and the difficulty of remediation once a problem has been identified.[40]

31. In addition, a National Research Council report on genetically modified pest-protected plants recommended research to better understand ecological effects, including detecting ecological impacts that "may not be predicted during the regulatory process".[41] Similarly, a National Research Council report on biological confinement of GMOs stated:

> More data are needed on the nature of potential ecological effects: their probability, their severity, and the potential for remedial action should confinement fail. Those research needs also were identified in recent [National Research Council reports] that noted the need for developing deeper theoretical and empirical understanding of the kinds of environmental effects that could result from transgene movement and the conditions under which such effects would be likely to occur.[42]

32. Each of these reports was prepared by a committee of impartial experts deliberating according to a well-established protocol and subjected to rigorous peer-review before publication. Their conclusion is that, at least until considerable experience is gained through testing a particular GMO, substantial uncertainty exists regarding the effect it will have on the environment and thus how it should be regulated.[43]

33. In sum, substantial uncertainty exists regarding the effects GMOs may have on plant, animal and human health (and on the environment as a whole)—uncertainty that is relevant to regulators, consumers, and citizens generally.

## III. Legal arguments

34. Article 5.7 is not an exception within the SPS Agreement. It is one of the Members' basic rights in the SPS Agreement's comprehensive approach towards ensuring that no Member is prevented from adopting or enforcing measures necessary to protect human, animal or plant life or health.[44] Under the SPS Agreement, Members have the right to determine the level of protection they find appropriate within their territories and to take measures to attain and maintain that level of protection.[45] Article 5.7 allows Members to take provisional measures when scientific evidence is insufficient

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[40] National Research Council, Animal Biotechnology: Science-Based Concerns 9 (The National Academies Press 2002).

[41] National Research Council, Genetically Modified Pest-Protected Plants: Science and Regulation 10-11 (The National Academies Press 2000).

[42] National Research Council, Biological Confinement of Genetically Engineered Organisms 196 (2004).

[43] In the analogous situation of non-indigenous species, another National Research Council report (Predicting Invasions of Non-indigenous Plants and Plant Pests – 2002) reached similar conclusions. For instance, it stated "there are currently no known broad scientific principles or reliable procedures for identifying the invasive potential of plants, plant pests, or biological control agents in new geographic ranges." While not all, or even most GMOs will become invasive species, the point is that scientists lack the tools to predict which non-indigenous species—and which GMOs—will become invasive, resulting in substantial uncertainty.

[44] SPS Agreement, *supra* note 5, at Articles 2.1 and 3.3.

[45] *Id.* See also Preamble.

for an adequate assessment of the risks and thereby safeguards their right to protect their citizens and the environment under those circumstances. Thus, the interpretation of the requirements that must be met in order for Members to adopt a measure under Article 5.7 directly affects the ability of countries to respond effectively to health and environmental needs.

35. One of these requirements in Article 5.7 is that provisional measures can only be imposed in situations where "relevant scientific information is insufficient,"[46] a key issue in the present case. The United States and Canada have both argued that the EC measures have been taken with no basis on scientific principles, in violation of Articles 2.2 and 5.1 of the SPS Agreement.[47] As Article 5.7 is intrinsically linked to those articles, it will most likely also be considered by the Panel. Moreover, the question of sufficiency of the scientific evidence will be particularly relevant in the context of GMOs. The uncertainty as to the effects of GMOs on human, animal, and plant life and health and its role in the determination of whether scientific evidence is insufficient, specifically, will be a fundamental concern. In Japan – Apples, the Appellate Body stated that "scientific uncertainty" is not the same as "insufficient scientific evidence," but it did not clarify the influence of uncertainty in determining whether the scientific evidence is insufficient in a given situation.[48] Since it is not infrequent that scientific information on a particular topic is inconclusive and the requirements of Article 5.7 are cumulative, the interpretation of "insufficient scientific evidence" will be relevant in any future SPS cases involving precautionary measures. Thus, it will significantly impact Members' right to adopt the measures necessary to protect the life and health of their citizens, animals, and plants.

## A. Uncertainty is a critical factor in determining when scientific evidence is insufficient under Article 5.7.

### 1. Uncertainty and the quality of scientific evidence

36. Uncertainty may not allow, in qualitative terms, the performance of an adequate risk assessment, thus making the scientific evidence "insufficient" within the meaning of Article 5.7.[49] Since the terms of a treaty must be interpreted in their context and in light of the treaty's object and purpose,[50] "insufficient scientific evidence" under Article 5.7 has never been read to refer to the mere quantity of relevant scientific information. In the range of measures allowed to Members by the SPS Agreement to protect and improve the human health, animal health and phytosanitary situation in their territories, Article 5.7 encompasses situations where science does not provide all the answers. Thus, Panels have recognized that, in certain cases, much scientific research may be carried out

[46] Japan – Measures affecting Agricultural Products (Japan – Varietals), WTO Docs. WT/DS76/AB/R (February 22, 1999), at para 89

[47] *See, e.g.,* the US first submission in EC-Biotech at paragraphs 109, 150 and 173 and the Canadian first submission in EC-Biotech at paragraph 269.

[48] Japan – Apples, *supra* note 6, at para. 184

[49] *Id.,* at para. 179.

[50] Vienna Convention on the of the Treaties (Vienna Convention), adopted on May 22, 1969, *available at* www.un.org/law/ilc/texts/treatfra.htm, at Article 31 (1).

yielding little or no reliable evidence.[51] In those cases, the quality of scientific evidence does not permit Members to make an adequate assessment of risks and such insufficiency entitles them to adopt precautionary measures.[52]

37. In this regard, uncertainty is a critical factor in determining the quality of the relevant scientific evidence. In fact, uncertainty may be thought of as a continuum ranging from zero for certain information to intermediate levels for information with statistical uncertainty (where an event has a known probability) to high levels for information with true uncertainty or indeterminacy (where an event has an unknown probability).[53] Uncertainty is a given in any scientific inquiry, which can only establish the boundaries of existing knowledge, and thus will not always trigger the need for precautionary action. However, when the available information cannot appropriately describe the risks to human, animal, or plant life or health because of the lack of understanding of events and processes, policy-makers cannot ignore the lack of quality of the scientific evidence. One such regulatory response to insufficient evidence stemming from the lack of quality of available information is Article 5.7. Therefore, while uncertainty does not in itself trigger Article 5.7, it constitutes an essential element in determining whether or not the quality of the scientific evidence is sufficient for an adequate assessment of risks

## 2. Uncertainty and the right to choose an appropriate level of protection

38. Failing to consider scientific uncertainty, such as that described in Section II of the present brief, in the context of Article 5.7 would not only unduly limit the measures available to Members under the SPS Agreement, but would also undermine the basic right of Members to protect their citizens and their environments within the chosen parameters. As a fundamental element of the object and purpose of the SPS Agreement, the right to determine an "appropriate level of sanitary or phytosanitary protection" must be a key consideration in interpreting Article 5.7. In that regard, the Appellate Body has recognized that Members have an autonomous right to determine the level of risk they consider acceptable within their territory, which may even consist of "zero risk."[54]

39. Given the inherent relationship between the right to determine an objective – a country's appropriate level of sanitary and phytosanitary protection – and the measures chosen to attain or implement it,[55] provisions dealing with these measures must safeguard the Members' prerogatives in relation to the chosen level of protection. If uncertainty is not considered in the determination of whether scientific evidence is insufficient under Article 5.7, Members would be forced to make decisions on the basis of information that cannot ascertain the risks to human, animal, or plant life or health in a manner adequate to the level of protection chosen by the Member. In other words,

[51] Japan – Apples, *supra* note 6, at para. 179.
[52] *Id.*
[53] *See* Robert Costanza and Laura Cornwell, *"The 4p Approach to Dealing with Scientific Uncertainty,"* in ENVIRONMENT, Volume 34, Number 9, November 1992.
[54] Australia – Measures Affecting Importation of Salmon (Australia – Salmon), WTO Docs. WT/DS18/AB/R (October 20, 1998), at para. 125.
[55] *Id., at para 200.*

Members would be deprived of the right to establish the level of protection they deem appropriate for their territory.

40. In the *EC-Biotech* case, for example, the technology at issue involves scientific uncertainty directly relevant to regulators. Science is inconclusive regarding the ultimate characteristics of GMOs, their effects on human, animal, and plant life and health, and other aspects crucial for a proper evaluation of risks. Such critical scientific uncertainties significantly affect the sufficiency of scientific evidence under Article 5.7. In regulatory systems based on a low level of acceptable risk, such as the system in force in the EC, the uncertainty described in Section II clearly demonstrates that scientific evidence is not sufficient in quality, as it does not produce reliable or conclusive results, to assess the risks in a manner adequate to the chosen level of protection. Consequently, the first condition under Article 5.7, the "insufficiency" of relevant scientific evidence, is met by the EC measures challenged in the present case.

## B. Uncertainty is a critical factor in determining the application of the precautionary principle in relevant international law.

41. WTO rules cannot to be read in clinical isolation from public international law.[56] Customary rules of interpretation of public international law, recognized by the WTO dispute settlement system, require that WTO agreements be considered as a part of the broader corpus of international law and principles.[57] Moreover, the Appellate Body has emphasized the importance, in certain circumstances, of interpreting terms in the WTO Agreements in light of the "contemporary concerns of the community of nations."[58] Such an approach ensures the development of a coherent system of international law, which in turn, promotes respect for the international system in general.[59]

42. International law and principles may provide particularly significant interpretative guidance to the Panel in the present case for two reasons. First, the concerns of the international community regarding the transboundary movement of GMOs are reflected in the first comprehensive international agreement on the subject at issue, the Cartagena Protocol on Biosafety (Biosafety Protocol), which recently entered into force.[60] Second, the precautionary principle reflected in the SPS Agreement, and particularly in Article 5.7, provides critical interpretative guidance for regulators and adjudicators in cases

[56] United States of America – Standards for Reformulated Gasoline and Conventional Gasoline (USA - Gasoline), WTO Docs. WT/DS2/AB/R, (April 29, 1996), at page 17.

[57] DSU, *supra* note 1, at Art.3.2. Article 3(2) of the DSU states that the dispute settlement system serves to clarify the provisions of WTO agreement "in accordance with customary rules of interpretation of public international law." The interpretation rules of the Vienna Convention, generally considered customary law, provide that "any relevant rules of international law applicable between the parties" be taken into account in the interpretation of treaties.

[58] United States – Import Prohibition of Certain Shrimp and shrimp Products (USA – Shrimp Turtle), WTO Docs. WT/DS58/AB/R, (October 12, 1998), at para. 129

[59] *See, e.g.*, Gabrielle Marceau, "WTO Dispute Settlement and Human Rights," European Journal of International Law Volume 13, Issue 4, September 2002: pp. 753-814 .

[60] the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (Biosafety Protocol) adopted in Montreal on January 29, 2000, *available at* www.biodiv.org/biosafety/protocol.asp., at Article 1. The Biosafety Protocol came into force on September 11, 2003..

where uncertainty renders scientific evidence insufficient to adequately determine sanitary and phytosanitary risks.

43. Uncertainty is a key element in the Biosafety Protocol. In fact, it was the relative novelty and lack of experience with the genetic modification of organisms that catalyzed the negotiation of the Biosafety Protocol.[61] The precautionary principle is thus incorporated in several operative provisions.[62] Article 10, for instance, establishes that in the main decision procedure under the Biosafety Protocol, the "lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects" of a genetically modified organism[63] does not prevent Parties from adopting the necessary measures to avoid or minimize potential adverse effects. Other provisions similarly recognize the link between insufficient scientific information and uncertainty.[64] Even if in the context of the SPS Agreement, uncertainty does not – as in the Biosafety Protocol – trigger precaution in itself, it is clear that the link between uncertainty and precaution has been established by relevant rules of international law, and thus cannot be overlooked.

44. Scientific uncertainty is an essential component of the precautionary principle. In fact, it was the recognition that science does not have all the answers in certain circumstances that led to the acknowledgement that uncertainty could not be used to postpone measures to respond to serious and complex health and environmental problems and the development of the precautionary principle.[65] Even now, while the precautionary principle may be worded differently in various instruments – not an uncommon characteristic in international customary law – the notion of inconclusive scientific evidence is at the core of each statement. In that regard, the 1992 Rio Declaration on Environment and Development, for instance, an instrument that the United States has signed,[66] states that "where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." The influence of uncertainty in justifying precautionary measures should thus be equally considered in the interpretation of Article 5.7.

## IV. Conclusion

45. The present amicus curiae brief presents considerable scientific evidence as to the uncertainty involved in evaluating the risks of GMOs to human, animal, and plant life and health. The uncertainty is, in fact, so substantial that it impedes any adequate

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[61] Mackenzie R., Burhenne- Guilmin F., La Viña A. and Werksman J.:*"An Explanatory Guide to the Cartagena Protocol on Biosafety"* IUCN Environmental Policy and Law Paper (IUCN paper) No. 46, at page 13, para. 65.

[62] The precautionary principle is referenced in the Articles 1, 10 and 11, as well as in the Preamble and Annex III (4) on risk assessment.

[63] The Biosafety Protocol uses the term "living modified organisms," which in fact is narrower than the more general "genetically modified organisms."

[64] *See, e.g.,* Biosafety Protocol, *supra* note 30 at Article 11.8.

[65] David Appell, "The New Uncertainty Principle," *Scientific American,* January 2001.

[66] As a non-binding guideline, it did not require Senate ratification.

consideration of those risks. Thus, it is precisely the situation provided for in Article 5.7 of the SPS Agreement. Uncertainty, in other words, constitutes a crucial element in determining when there is "insufficient scientific evidence" under Article 5.7. In this way, Article 5.7 can fulfill its role of safeguarding the basic right of Members to protect their citizens and the environment, as well as their right to establish the level of protection they deem adequate. Nevertheless, even if the relationship between uncertainty and insufficient scientific evidence was unclear in the SPS Agreement, relevant rules and principles of international law, which the Panel may then turn to, support such an understanding of the role of uncertainty in taking precautionary measures, particularly in the context of GMOs.