



**Food and Agriculture Organization
of the United Nations**



World Health Organization

Biotech 00/05

**Joint FAO/WHO Expert Consultation on Foods Derived from
Biotechnology**

**Headquarters of the World Health Organization
Salle G
Avenue Appia 20, 1211 Geneva 27, Switzerland
29 May – 2 June 2000**

**Topic 3: Limitation of Substantial Equivalence Regarding the Assessment
of Foods Derived from Biotechnology**

**Eric Brunner, University College London
United Kingdom**

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This article appeared as a commentary in NATURE 1999, VOL 401, PP 525-26

The subsequent correspondence is not discussed.

BEYOND 'SUBSTANTIAL EQUIVALENCE'

Erik Millstone, Eric Brunner and Sue Mayer

SHOWING THAT A GENETICALLY MODIFIED FOOD IS CHEMICALLY SIMILAR TO ITS NATURAL COUNTERPART IS NOT ADEQUATE EVIDENCE THAT IT IS SAFE FOR HUMAN CONSUMPTION.

Whenever official approval for the introduction of genetically modified (GM) foods has been given in Europe or the United States, regulatory committees have invoked the concept of 'substantial equivalence'. This means that if a GM food can be characterized as substantially equivalent to its 'natural' antecedent, it can be assumed to pose no new health risks and hence to be acceptable for commercial use. At first sight, the approach might seem plausible and attractively simple, but we believe that it is misguided, and should be abandoned in favour of one that includes biological, toxicological and immunological tests rather than merely chemical ones.

The concept of substantial equivalence has never been properly defined; the degree of difference between a natural food and its GM alternative before its 'substance' ceases to be acceptably 'equivalent' is not defined anywhere, nor has an exact definition been agreed by legislators. It is exactly this vagueness which makes the concept useful to industry but unacceptable to the consumer. Moreover, the reliance by policymakers on the concept of substantial equivalence acts as a barrier to further research into the possible risks of eating GM foods.

Acceptable daily intake

The concept of substantial equivalence emerged in response to the challenge confronting regulatory authorities in the early 1990s. Biotechnology companies had developed several GM foods and, to reassure their customers, wanted official approval for their introduction. But government statutes did not cover GM foods, nor provide the authority to regulate these innovations. Legislation could be amended, but that would not address the core problem of how to assess the risks. One obvious solution at that time would have been for legislators to have treated GM foods in the same way as novel chemical compounds, such as pharmaceuticals, pesticides and food additives, and to have required companies to conduct a range of toxicological tests, the evidence from which could be used to set 'acceptable daily intakes' (ADIs). Regulations could then have been introduced to ensure that ADIs are never, or rarely, exceeded.

From the point of view of the biotechnology industry, this approach would have had two main drawbacks. First, companies did not want to have to conduct toxicological experiments, which would delay access to the marketplace by at least five years, and would add approximately \$25 million per product to R&D costs. Second, by definition, using ADIs would have restricted the use of GM foods to a marginal role in the diet. An ADI is usually defined as one-hundredth of the highest dose shown to be harmless for laboratory animals.

Thus, even if laboratory animals show no adverse effects on a diet consisting exclusively of a test material, human intake would still be restricted to 1% of the human diet. The biotechnology companies want to market GM staples, such as grains, beans and potatoes, which individually might account for as much as 10% of the human diet, and collectively might provide more than half of a person's food intake.

The adoption of the concept of substantial equivalence by the governments of the industrialized countries signalled to the GM food industry that as long as companies did not try to market GM foods that had a grossly different chemical composition from those of foods already on the market, their new GM products would be permitted without any safety or toxicology tests. The substantial-equivalence concept was also intended to reassure consumers, but it is not clear that it has served, or can serve, that purpose. Although toxicological and biochemical tests, and their interpretation, are notoriously problematic and contested, and are slow and expensive, they can provide information vital to consumer protection.(1)

Trying to have it both ways

The challenge of how to deal with the issue of risk from consuming GM foods was first confronted in 1990 at an international meeting, consisting of officials and industrialists but no consumer representatives, of the UN Food and Agriculture Organisation (FAO) and the World Health Organisation (WHO).(2) The FAO/WHO panel report makes intriguing reading, because what it fails to mention is as important as what is discussed. It does not use the term 'substantial equivalence' or mention ADIs. It implies that GM foods are in some important respects novel, but it then argues that they are not really novel at all – just marginal extensions of traditional techniques. These inconsistencies are inevitable, given that the industry wanted to argue both that GM foods were sufficiently novel to require new legislation and a major overhaul of the rules governing intellectual property rights to allow them to be patented, yet not so novel that they could introduce new risks to public or environmental health.

The biotechnology companies wanted government regulators to help persuade consumers that their products were safe, yet they also wanted the regulatory hurdles to be set as low as possible. Governments wanted an approach to the regulation of GM foods that could be agreed internationally, and that would not inhibit the development of their domestic biotechnology companies. The FAO/WHO committee recommended, therefore, that GM foods should be treated by analogy with their non-GM antecedents, and evaluated primarily by comparing their compositional data with those from their natural antecedents, so that they could be presumed to be similarly acceptable. Only if there were glaring and important compositional differences might it be appropriate to require further tests, to be decided on a case-by-case basis.

Unfortunately, scientists are not yet able reliably to predict the biochemical or toxicological effects of a GM food from a knowledge of its chemical composition. For example, recent work on the genetics of commercial grape varieties shows that, despite detailed knowledge going back for centuries of the chemistry and flavour of grapes and wines, the relationship between the genetics of grapes and their flavour is not yet understood (3). Similarly, the relationship between genetics, chemical composition and toxicological risk remains unknown. Relying on the concept of 'substantial equivalence' is therefore just wishful thinking: it is tantamount to pretending to have adequate grounds to judge whether or not products are safe.

The results of Arpad Pusztai's experiments with GM potatoes and their interpretation remain a matter of controversy (4), but his starting hypothesis was that GM potatoes would be substantially equivalent to non-GM potatoes. Pusztai interpreted his still unpublished results as indicating that the GM potatoes exerted adverse biochemical and immunological effects, which could not have been predicted from what was known of their chemical composition. The kinds of experiments which he conducted are not legally required and are therefore not routinely conducted before GM foods are introduced into the food chain.

'Substantial equivalence' ill-defined

The concept of 'substantial equivalence' was first introduced in 1993 by the OECD (5), and was subsequently endorsed in 1996 by the FAO and WHO. Given the weight the concept has been required to carry, it is remarkable how ill-defined it remains, and how little attention has been devoted to it. The OECD document states:

"For foods and food components from organisms developed by the application of modern biotechnology, the most practical approach to the determination is to consider whether they are substantially equivalent to analogous food product(s) if such exist....The concept of substantial equivalence embodies the idea that existing organisms used as foods, or as a source of food, can be used as the basis for comparison when assessing the safety of human consumption of a food or food component that has been modified or is new."

That is the closest there has been to an official definition of substantial equivalence, but the definition is too vague to serve as a benchmark for public health policy.

GM glyphosate-tolerant soya beans (GTSBs) illustrate how the concept has been used in practice. The chemical composition of GTSBs is, of course, different from all antecedent varieties, otherwise they would not be patentable, and would not withstand the application of glyphosate. It is quite straightforward to distinguish, in a laboratory, the particular biochemical characteristics which make them different. GTSBs have, nonetheless, been deemed to be substantially equivalent to non-GM soya beans by assuming that the known genetic and biochemical differences are toxicologically insignificant, and by focusing instead on a restricted set of compositional variables, such as the amounts of protein, carbohydrate, vitamins and minerals, amino acids, fatty acids, fibre, ash, isoflavones and lecithins. GTSBs have been deemed to be substantially equivalent because sufficient similarities appear for those selected variables.

But this judgement is unreliable. Although we have known for about 10 years that the application of glyphosate to soya beans significantly changes their chemical composition (for example the level of phenolic compounds such as isoflavones (6), the GTSBs on which the compositional tests were conducted were grown without the application of glyphosate (7). This is despite the fact that commercial GTSB crops would always be treated with glyphosate to destroy surrounding weeds. The beans which were tested were, therefore, of a type which would never be consumed, while those which are being consumed were not evaluated. If the GTSBs had been treated with glyphosate before their composition was analysed it would have been harder to sustain their claim to substantial equivalence. There is a debate in the research community on whether such changes to the chemical composition are desirable or undesirable, but it is an issue which remains unresolved, and which has been neglected by those who have deemed GTSBs and non-GM soybeans to be substantially equivalent.

Only one official organization has recognized some of the limitations of the concept of substantial equivalence. A Dutch government team has acknowledged that "compositional analysis...as a screening method for unintended effects...of the genetic modification has its limitations. in particular regarding unknown anti-nutrients and natural toxins", and it has given a lead by trying to explore some alternatives (8). The Dutch team accepts that comparisons of relative crude compositional data provide a very weak screen against the introduction of novel genetic, biochemical, immunological or toxicological hazards, and they have suggested a finer-grained screen to test for differences in some of the relevant biological variables, such as DNA analysis, messenger-RNA fingerprinting, protein fingerprinting, secondary metabolite profiling and in vitro toxicity testing. If the use of such a finer screen revealed that a GM food contained a relevant novelty then the case for further studies would be far stronger, and those studies might benefit from having some clues as to which end-points might be most worthy of investigation.

An anti-scientific test

Substantial equivalence is a pseudo-scientific concept because it is a commercial and political judgement masquerading as if it were scientific. It is, moreover, inherently anti-scientific because it was created primarily to provide an excuse for not requiring biochemical or toxicological tests. It therefore serves to discourage and inhibit potentially informative scientific research. The case of GTSBs shows, moreover, that the concept of substantial equivalence is being misapplied, even on its own terms, within the regulatory process. If policymakers are therefore to provide consumers with adequate protection, and genuinely to reassure them, then the concept of substantial equivalence will need to be abandoned, rather than merely supplemented. It should be replaced with a practical approach which would actively investigate the safety and toxicity of GM foods rather than merely taking them for granted, and which could give due consideration to public health principles as well as to industrial interests.

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Erik Millstone is at SPRU-Science and Technology Policy Research, Mantell Building, Sussex University, Brighton BN1 9RF, UK.

Eric Brunner is in the Department of Epidemiology and Public Health, University College, 1-19 Torrington Place, London WC1E 6BT, UK.

Sue Mayer is at GeneWatch UK, The Courtyard, Whitecross Road, Tideswell, Buxton, Derbyshire SK17 8NY, UK.

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