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ASSESSMENT OF GM CROPS IN COMMERCIAL AGRICULTURE

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ABSTRACT. The caliber of recent discourse regarding genetically modified organisms (GMOs) has suffered from a lack of consensus on terminology, from the scarcity of evidence upon which to assess risk to health and to the environment, and from value differences between proponents and opponents of GMOs. Towards addressing these issues, we present the thesis that GM should be defined as the forcible insertion of DNA into a host genome, irrespective of the source of the DNA, and exclusive of conventional or mutation breeding.

Some defenders of the commercial use of GMOs have referred to the scientific work of GMO critics as "junk science." Such a claim is false and misleading, given that many papers critical of both the utility and safety of GMOs have been published in peer reviewed journals by respected scientists. In contrast, there is a dearth of peer reviewed work to substantiate the frequently heard assertions of either safety or utility in GMOs. The polarity, which now characterizes much of the public discourse on GMOs, reflects not simply scientific disagreement, but also disagreement in underlying value assumptions. Value differences strongly affect the assessment of both benefit and harm from GMOs.

The concept of substantial equivalence occupies a pivotal position in the GMO risk assessment process that is used in both Canada and the US. A GMO judged to be substantially equivalent to a conventional product – as have all submissions to date – is presumed to be safe enough for commercialization. The conclusion of safety – from both human health and environmental perspectives – should be based on scientific evidence, corroborated by actual experimentation. However, regulators infer safety largely from assumptions-based reasoning, with little or no experimental validation. The judgement of safety because of substantial equivalence is a dubious argument by analogy.

KEY WORDS: biotechnology, genetic engineering, junk science, risk assessment, substantial equivalence

INTRODUCTION

We understand *genetically modified organisms* (*GMO*) to be organisms that are produced by the forcible insertion of DNA into a host genome. Because alien DNA has introgressed across species boundaries throughout evolution, and because many of the unpredictable side-effects of transgene insertion are comparable when endogenous as well as transgenes are inserted (e.g., Napoli et al., 1990; Bergelsen et al., 1998), the distinguishing feature of *genetic modification* (*GM*) is forcible gene insertion *per*

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se, not the wideness of the cross. Corn that has been genetically modified by inserting bacterial genes to produce Bt, an endotoxin that is lethal to European corn borers, is an example of a GMO. Many GM organisms have been produced, including bacteria, fungi, insects, fish (Muir and Howard, 1999), mammals, and trees (Tommeras and Hindar, 1999), as well as crop plants. Some have been commercialized in crops of corn, soybeans, canola, cotton, and other crops, while most are still pending (Table I).

Discussion of issues with which we are concerned may be clouded by terminology. Terms such as *biotechnology*, *genetic engineering*, and *genetic modification* are often, though not always, used interchangeably to refer broadly to the use of modern genetics in agricultural technology. Clearly the term *biotechnology* can readily be given a much broader connotation than the other terms. Cloning, mutation breeding, and conventional plant breeding are other processes in which genetics has been put to practical agricultural use. However, genetic modification through insertion of transgenes introduces issues and risks that are distinct from those of other processes. Therefore, in this paper, we will focus on controversies concerning genetic modification of agricultural crops, which we will call *genetic modification* or *genetic engineering*.

In the following discussion, we use the terms "proponents" and "opponents" of genetic modification. Neither opponents nor proponents of genetic engineering are homogenous groups of people. Each group includes people who are driven by a number of distinct motivations. Proponents of genetic engineering include people motivated directly by commercial interests, or indirectly, by the research funding, joy of discovery, power, and prestige that are afforded by the commercialization of their work. Opponents of genetic engineering of new crops may also include people motivated by commercial interests, such as a competing agribusiness firm whose herbicidal product line is being encroached upon by the proprietary herbicide-tolerant crop line of other firms. Proponents of genetic engineering often appear to include people who are unreflectively committed to the view that GM is progressive and thus beneficial to agriculture. Opponents of genetic engineering may include people who unreflectively regard GM crops as inherently harmful, or who see it as a means of prolonging dependence on resource-intensive, environmentally harmful methods of crop production.

However, some GM supporters have suggested that to be opposed to the immediate commercial deployment of genetically engineered crops is to be a "Luddite," opposed to all scientific knowledge and the benefits that may derive therefrom. Opponents to the immediate deployment of genetically engineered crops are judged to be unscientific fools or anti-scientific

TABLE I

Overview of the traits that have been introduced into GM plants (adapted from Madsen and Poulsen (1997)

Type of tolerance	Specific application	Comments
Herbicide	Glyphosate	Non-selective, broad spectrum herbicide; inhibits EPSPS enzyme of the shikimic acid pathway that produces phenylalanine, tyrosine, and tryptophane; e.g., Roundup
	Glufosinate ammonium	Non-selective, broad spectrum herbicide; inhibits glutamate synthase, an enzyme involved in assimilation of ammonia and regulation of N metabolism; the only enzyme which detoxifies ammonia; e.g., Liberty
	Bromoxynil	Post-emergence herbicide for dicot weeds; acts as potent inhibitor of electron transport at the photosystem II site; also, uncouples oxidative and PS phosphorylation; e.g., BXN cotton
	ALS-inhibitors	Broad spectrum, high efficacy, low rate herbicide; ALS (acetolactate synthase) inhibitors, including the commercialized sulfonylureas and imidazolinones ("imi's"), block ALS, an enzyme in synthesis of branched-chain amino acids: valine, leucine, and isoleucine; the trait is naturally occurring and can be induced by mutation, as well as transformation; widespread resistance to ALS has already developed in target weed species; e.g., Pursuit
	Others	Not all herbicide tolerance is genetically engineered; triazine resistance, for example, is conferred by a naturally occurring mutant chloroplast gene – although in this case, there was a significant yield penalty associated with the transgene
Insect tolerance	Bt	Highly selective, naturally occurring insecticide, although selectivity appears to be lost when introduced transgenically; crystals formed during sporulation of *Bacillus thuringiensis*, a soil microbe, contain proteins (-endotoxins) that become toxic when ingested by particular classes of insects; endotoxins and their target organisms are CryI – lepidopterans; CryII – lepidopteran and dipterans; CryIII – coleopterans; CryIV – dipterans, and CryV – lepdopteran and coleopteran species
	Protease inhibitors	Antimetabolic proteins, causing mortality, decreased growth, and prolonged larval development due to malnutrition, e.g., naturally occurring cowpea trypsin inhibitor (CpT1), which when inserted transgenically into tobacco, confers tolerance to tobacco budworms (*Heliothis virescens*)
	Amylase inhibitors	Insecticidal properties from inhibition of amylases in midgut, causing retarded growth; naturally occurring in common bean, when transferred transgenically to peas, confers resistance to cowpea weevils (*Callosobruchus masculatus*) and azuki bean weevils (*C. chinensis*) during storage and growth
	Lectin proteins	Carbohydrate-binding plant proteins, similar to protease and amylase inhibitors; different plant families produce different lectins; e.g., the snowdrop lectin (GNA) of Ewen and Pusztai (1999) protects transgenic tobacco, potatoes, and lettuce against sap-sucking insects, as peach potato aphid (*Myzus persicae*)
Virus tolerance	Coat proteins, satellite RNAs, replicase, antisense, defective interfering, Cis-acting elements, movement protein, ribozymes	
Fungal tolerance	Phytoalexins, ribosome inactivation proteins, chitinases, and glucanases	
Bacterial tolerance	Lysozymes, lytic peptides, toxins, H_2O_2	
Flower characteristics	*Pigmentation changes, as in flavonoids, carotenoids, and betalains, to produce orange petunia, blue rose, violet carnation, etc. *Male sterility in *Brassica sp.*	
Metabolic content	Alterations of existing compounds (protein, oil, carbohydrates) or synthesis of novel compounds (e.g., molecular farming), as for carbohydrates, fatty acids, pharmaceuticals (e.g., vaccines; interleuken-6), industrial enzymes, and biodegradable plastics	
Stress tolerance	*Drought tolerance (e.g., elevated concentrations of proline or fructans to enhance osmolality) in tobacco *Oxidatative stress tolerance, via anti-oxidant enzyme overexpression, conferring drought or chilling tolerance in tobacco, alfalfa, and cotton *Cold tolerance in tomato and tobacco *Salinity tolerance in tobacco	

ideologues. For example, Powell (1999) referred to GMO critics as "having side-stepped the science and cloaked themselves as defenders of all that is natural and pure, these groups will spout lies, ranging from blatant admissions of fact to conspiracy theories woven from tidbits drawn from wherever is convenient." This is a mistaken opinion. As we will argue below, a growing body of accomplished scientists are concerned about the immediate use of GM because they believe that we do not have enough scientific knowledge to do so without undue risk of serious harm. Some scientists may oppose the commercialization of GM crops now, without maintaining that GM crops should never be used. That is, opposition to GM may pertain to the specific current applications of GM technology, or the manner in which human and environmental risks are being assessed, without necessarily reflecting opposition to genetic engineering in principle. Conversely, some scientists who are comfortable with current GM offerings have significant concern about the more complex and less studied GM products currently in development, such as using Bt-corn to address corn rootworm.

ROOTS OF CONTROVERSY

Considerable controversy surrounds GM crops, as reported in the popular media as well as in scientific papers. Supporters of GM crops point to many potential benefits, such as higher yields, lesser reliance on biocides, and increasing stress tolerance to widen the zone of adaptation of crops. They further allege that GM crops pose no risks to either human health or the environment. Critics challenge the degree to which the purported benefits have, in fact, been realized in practice (Clark, 1999; Benbrook, 1999). They also identify potential harms that may derive from GM crops, such as damage to beneficial insects and soil organisms (Altieri, 2000), the unfairness of externalizing costs of production to neighboring farmland through genetic pollution, the enhancement of antibiotic resistant diseases (Teuber, 1996), and the involuntary exposure of humans, livestock, and wildlife to undetected toxins, allergens, and other compounds. Rissler and Melon (1996) ask, for example, what happens to wildlife that consumes alfalfa producing "anti-cancer drugs, growth hormones, and vaccines . . ." Critics allege that we do not yet have adequate scientific knowledge to provide rational warrant for accepting the claim that use of GM crops is safe for human consumption and for the environment.

A major issue in this controversy is whether the production of GM crops at the present time is ethically acceptable. In other words, should modern society directly or indirectly oblige farmers to discontinue production of

GM crops pending further scientific analysis of their potential benefits and harms? Some of those who maintain that it is acceptable, or even necessary, to proceed now with the deployment of GM crops have expressed the view that we already have scientific proof that GM crops are acceptably safe. Characteristic of the genre is a contribution from a group of Canadian academics who stated that "there is a wealth of peer-reviewed, publicly available information regarding safety assessments of genetically engineered foods . . ." (Ellis et al., 1999). In more temperate terms, Dale (1999) stated that to inhibit the development of GM crops "would make a generic negative judgement about a whole area of scientific enquiry and development."

Despite the confidence of these learned scholars, do we in fact know enough to allow this technology to continue to operate globally? Domingo (2000) attempted to gauge the depth of scientific understanding of GM food safety issues, using the Medline database (available at *http://www.ncbi.nlm.nih.gov/pubmed/*) (Table II).

TABLE II

Opinions vs. experimentation in the refereed literature on GM food safety (adapted from Domingo, 2000)

Base phrase for Medline Database search	Total number of identified citations	Number of citations specifically related to the question	
		Citations reporting experimentation	Citations of opinion, sans experimentation
"Toxicity of transgenic foods"	44	1	7
"Adverse effects of transgenic foods"	67	2	16
"Genetically modified foods"	101	6	37

The three search phrases in Table II identified a total of eight different experimental studies regarding the safety of GM products: one on mice (Fares and El-Sayed, 1998), one 38-day feeding trial on Bt corn in broiler rations (Brake and Vlachos, 1998), two studies on GM soybeans on rats (Onishchenko et al., 1999; Tutelian et al., 1999), two studies of GM lectin with rats (Ewen and Pusztai, 1999) and human blood cells (Fenton et al., 1999), and two other studies relating to digestion of transgenes in rats and other animals (Hammond et al., 1996; Schubbert et al., 1997). According to this database search, eight, largely rodent-based assessments are the sum total of peer-reviewed information available on the safety of GM foods. We are aware of two other relevant rat digestion papers from the Schub-

bert group in Germany (Doerfler and Schubbert, 1998; Schubbert et al., 1998), as well as a compositional paper from a Monsanto lab (Padgette et al., 1996). The near vacuum in refereed information on the safety of GM crops, particularly from independent (not industry) researchers, was in fact a key motivation for the research of Arpad Pusztai, at the Rowett Research Institute in Scotland, on transgenic potatoes containing snowdrop lectin (Ewen and Pusztai, 1999).

Irrespective of the paucity of published data, the database search also identified a total of 60 sets of authors who offered their opinions and commentaries, unsupported by data. Domingo (2000) noted that most were written by proponents of the safety of transgenic foods. He expressed surprise at the absence of citations of studies conducted by the GM companies themselves, and wondered why the evidence claimed by proponents of GM food safety had not been subjected to peer review and publication in the refereed journals. So, the question remains – how can we claim sufficient information to have confidence in the safety of GM food?

Commercial adoption of GM technology was not preceded by any rigorous and scientifically defensible assessment of benefits or harms for consumers or primary producers, for the Third World, for biodiversity, or for the environment. We do not believe any such integrated studies exist or are even contemplated by any organization with sufficient funds to pay for it. In the absence of any such thorough study, much of the recent argumentation on the matter has been logically unsound or even fallacious.

ARGUMENT BY ANALOGY: THE USE OF SUBSTANTIAL EQUIVALENCE

Many people, for example US Senator Christopher Bond (2000), insist that the government screening process for both the food safety and environmental risk of GM crops is thorough and rigorous. Perhaps Senator Bond and others may wish to learn more about the actual nature of the screening process as it is employed today.

In both the US and Canada, the regulatory process starts from the premise that a transgenic crop offered for commerce differs from an unmodified crop only in the trait coded for by the transgene (e.g., herbicide tolerance), and in all other respects, is “substantially equivalent” to the unmodified crop species. This presumption justifies the use of a few simple measurements and simple inductive reasoning to infer that GM crops are substantially equivalent to their non-GM counterparts. According to such reasoning, if crop A is like crop B in certain respects, and A is safe for humans to consume, then B is safe for humans to consume. Such reasoning

amounts to little more than argument by analogy. While such arguments have a role to play in suggesting hypotheses, normally scientists would not consider such inferences as confirming or corroborating. To corroborate or confirm an hypothesis H normally requires stronger statistically based inductive inferences that refute the null hypothesis.

Crops that have been found to be substantially equivalent – as have all GM crops submitted to date in both the US and Canada – are not required to undergo any more detailed testing (see below). Thus, apart from a few simple compositional measurements, the more detailed lab and animal trial parameters indicated for assessing safety of GM crops in Canada (Food Directorate, 1994) have never been operationalized, because they would be needed only for crops deemed not to be substantially equivalent.

To demonstrate substantial equivalence in toxicology and allergenicity, government regulators accept industry comparisons of the nucleotide (DNA) sequence of the *single target transgene* (only) and the amino acid sequence of the *single target protein* coded for by that transgene (only), with those in a computer database of known toxins and allergens. This – and only this – is what was done to test for toxicity in 70% of the 42 crops approved in Canada,[1] and to test for allergenicity in 100% of the approved crops (Clark, 2000).

For 1 of 1 soybean, 10 of 15 corn, and 1 of 4 potato submissions (30% of the 42 GM crops approved in Canada), government regulators accepted rat feeding trials in which the single, purified protein coded for by the transgene was fed for brief intervals to assess *acute* toxicity. They required no actual measurement of *chronic* toxicity, allergenicity, or any other kind of potential health risk factor. They did not require any whole grain feeding or performance trials (with 2 exceptions; see Clark, 2000) that might have revealed unintended side-effects, and hence, invalidated the presumption of substantial equivalence. With two exceptions, no evidence exists of trials to assess risks of feeding GM crop byproducts, such as soy or canola meal, to livestock.

Contrast this with the protocol required in Switzerland for the safety assessment of GM chymosin – a purified product that is used for coagulation of milk during cheese-making (Teuber, 1996). This protocol stipulates:

a) no GM organisms or recombinant DNA in the product;
b) no pathogenicity of producer microbes in experimental animals (mice) by intravenous, intraperitonal, nasal, cerebral, and subcutaneous application;

[1] Now 43.

c) no acute toxicity in rates (5 g cheese daily for 3 weeks; 5 g chymosin oral per kg);
d) no subchronic toxicity (100 mg chymosin per kg, 90-day test),
e) no allergenic sensibilization in Dunking-Harley-Pirbright test in guinea pigs;
f) no mutagenicity in Ames test for *Salmonella typhimurium*;
g) no cytotoxicity for human cell cultures

In both the US and Canada, government regulators do not conduct their own validation trials, nor allow any independent assessment of the quality or adequacy of industry submissions. And finally, they do not label GM foods, or conduct any post-approval monitoring of human health impacts. This is, in fact, the rigour with which the safety of GM foods is actually assessed prior to unconfined release into the marketplace of North America.

Environmental risk assessment of GM is an area that is equally in flux. As in the case of food safety testing, no consensus exists on how to conduct environmental risk assessment for GM crops, although numerous contributors are attempting to reach a better understanding of assessment protocols (e.g., Ammann et al., 1999; Traynor and Westwood, 1999).

Purrington and Bergelson (1995) discussed the protocol for assessing environmental risk of weediness under USDA APHIS (*United States Department of Agriculture, Animal and Plant Health Inspection Service*) guidelines. They noted first that "little guidance is offered as to the data that are acceptable," a statement that would apply equally well in Canada. They then analyzed the strength of petitions *already approved* for unconfined release. They observed that little in the way of quantitative data was provided by proponents on differences between transgenic and nontransformed lines. Furthermore, they argued, most of the evidence suffered from a critical experimental flaw, in which the parental variety was not used as a control. As a result, "investigators are unable to test the null hypothesis that plant performance is unchanged by the addition of a transgene."

They proposed a suite of 14 parameters[2] that would need to be measured – a potentially more predictive screen than the basic agronomic parameters used to assess risk under the current system. They further emphasized the need to measure performance not just of the transgenic line and its parents, but also that of reciprocal hybrids of the crops and weeds "even if sexually compatible relatives are rare or absent," specifically, "to evaluate the threat posed by the distribution of transgenic crops to foreign

[2] Seed viability, dormancy, production and dispersal; growth rate and period; clonal reproduction; lifetime survivorship; competitiveness; geographic range; pollen flow and performance; fitness of hybrids with other cultivars; fitness of hybrids with wild species.

countries that contain wild relatives yet often lack even rudimentary laws governing importation of biotechnology products."

Regrettably, GM research funding priorities – at least in the US and Canada – do not provide the opportunity for us, or others, to perform the research or provide the in-depth analysis needed to assess the potential risks and benefits of GM crops. Indeed, only 1% of the USDA biotechnology budget is mandated, under the 1990 Farm Bill, to support GM risk assessment research.

Nonetheless, we can address the unhealthy polarity that now characterizes discussions about GM crops. Specifically, we will comment on the manner in which some proponents of GM crops, and specifically those whose primary professional responsibility is to further the public good, have supported their views. For academic and government employees, failure to pursue discussion about GM crops in a rational fashion amounts to serious dereliction of duty. Specifically we want to comment on three ways in which supporters of GM crops have tried to advance their cause. First, they have challenged both the competence and the ethics of critics of GM technology by labeling their work as scientifically unsound or as **junk science** or **pseudo-science** (cited in Trewavas, 2000). Secondly, in the self-same arguments, they typically claim that the GM crops that have been approved by government regulators in the United States or Canada are safe. Such claims imply scientific proof of the safety of such products. Thirdly, they allege that the public should tolerate the production of GM crops and consume GM food crops by invoking the principle of substantial *equivalence*. We will argue that none of these approaches contribute constructively to the collegial dialogue that is urgently needed to address the issues of GM agriculture.

PART I

What are the nature and limitations of *sound science*? We take sound science to be the opposite of junk science. Sound science is an ideal. It is defined by reference to proper scientific method, including careful ways of posing questions, gathering evidence, and analyzing the evidence to support or reject an hypothesis. Proper ways of gathering evidence and analyzing data vary depending on many factors that affect the ways in which hypotheses are tested. The term junk science suggests such anomalies as twentieth-century astrology, phrenology, or creation science. Such work is junk for many reasons. Hypotheses are not rigorously tested. The researcher is committed in advance to his conclusions. Therefore he poses questions and musters evidence in ways that never put the

preferred conclusion in doubt. In junk science relevant data is ignored and hypotheses are defended by reasons that have no independent scientific warrant.

As we have said, sound science is an ideal. The degree to which actual scientific work approaches that ideal is often judged through peer review for publication in a scientific journal. To label research that identifies potential risks of GM crops as junk science, as have some GM proponents, is misleading. The inference that research that identifies potential risks diverges widely from the scientific ideal is challenged by the growing number of peer-reviewed articles that – unlike the purported evidence on GM food safety – have withstood the test of publication in refereed journals (Table III).

The reader is invited to check the references for the works listed in Table III. Consult the authors of the papers concerning their methodology. Critically discuss the methodology with the referees for the refereed papers cited in the table. Conduct your own experiments to test, validate, or challenge their findings. This is how new research findings are assessed, weighed, validated, or discarded, in the traditional collegial fashion. Failing to do these things, while continuing to ignore or castigate the work for challenging some aspect of GM crops, is to engage in name-calling, hardly a valid or rational way of supporting one's opinions. To say or infer that concerns about GM crops rest only on junk science, that is science that deviates widely from the ideals of sound science, is unwarranted.

PART II

Some proponents of GM crops have implied or openly stated that we have scientific knowledge that GM foods are safe for human consumption. In a recent public debate, Trewavas (2000) stated: "Planting this GM crop necessitates satisfying 50 pages of regulations, four years of safety tests, 3–4 committees for approval with detailed examination and at the end of the day the likelihood of getting your crop trampled by unthinking activists." The substance of such inferences of rigorous safety testing has already been questioned (Table II). However even had the testing been rigorously done, claims of food safety cannot be proven simply by the use of sound science.

We advance two arguments in support of this claim. First the claim that GM foods are safe for human consumption is a very sweeping generality. If, in the future, it is discovered that some groups of humans who consumed such products in sufficient quantity or over long enough periods of time were significantly harmed, the claim that such products

TABLE III

Partial listing of recent peer-reviewed challenges to the environmental risk

Discipline	Senior scientist	Findings	Reference
Entomology	Nicholas Birch, Scotland	GE lectin in potatoes radiates non-target multi-trophic effects on beneficials	Birch et al., 1999
	Angelica Hilbeck, Switzerland	GE insertion of Bt into corn removes selectivity, causing non-target multi-trophic impacts on beneficials	Hilbeck et al., 1998
	John Losey, Cornell	Bt pollen adversely affects Monarch butterflies	Losey et al., 1999
	Bruce Tabashnik, University of Arizona	Frequency of resistance alleles in Bt target populations is much higher than expected; Bt delays development time in Bt target pests – challenges refugia concept	Tabashnik et al., 1997 Liu et al. 1999
Ecological genetics	Joy Bergelson, University of Chicago	The environmental risk assessment process used in the US is fundamentally flawed; Unintended gene expression accompanies transgene insertion even within the same species – inserting HT also changed *Arabadopsis thaliana* from a selfing to an outcrossing species	Bergelson et al., 1998 Purrington and Bergelson, 1995
	Anne-Marie Chevre, France	Canola crosses readily with wild radish	Chevre et al., 1997
	Norm Ellstrand, University California, Riverside	Sorghum crosses readily with johnstongrass – one of 10 worst weeds in the world; of the 30 most important crops in the US, over half co-occur with at least one wild weedy relative in North America; sexual compatibility common; 12 of the 13 most important crops in the world hybridize with wild relatives somewhere in agriculture; affects weed aggressiveness and species extinction	Arriola and Ellstrand, 1996, 1997 Ellstrand et al., 1999; Klinger and Ellstrand, 1994
	T. R. Mikkelson, Denmark	Glufosinate-tolerance can transfer from oilseed rape (*Brassica napus*) (2n = 38 chromosomes) into a wild weedy relative (*B. campestris*) (2n = 20); two generations of crossing and backcrossing moved the transgene into fertile, *B. campestris*-like plants containing 20 chromosomes	Mikkelson et al., 1996
	Allison Snow, Ohio State University	Risk of transgene flow to weeds, evolution of pest resistance, and other risks cannot be extrapolated from small plot research; HT (from *Brassica napus*) exerts a negligible metabolic cost to wild *B. rapa* and can persist in the absence of selection	Snow and Palma, 1997; Snow et al., 1999
Microbial biology	Di Giovanni, USEPA, Oregon	GE industrial enzyme production by alfalfa affects soil rhizospheric organisms	Di Giovanni et al., 1999
	Kelly Donegan, Dynamac Corp, Oregon	GE cotton, potato, tobacco, and alfalfa (Bt, proteinase inhibitors, and industrial enzyme production) affect soil macro- and microbiota; genomic DNA as well as insecticidal properties of Bt can persist in the soil for months; GE crops exert unintended effects on soil biota	Donegan et al., 1997 various, reviewed in Donegan and Seidler, 1999
	Guenther Stotzky, NY University	GE Bt corn actively exudes toxin from the roots; active toxin persists in the soil for many months, retains insecticidal activity	Doyle et al., 1995; Crecchio and Stotzky, 1998; Tapp and Stotzky, 1998; Saxena et al., 1999

TABLE III

Continued

Discipline	Senior scientist	Findings	Reference
Molecular genetics	Mae Wan Ho of the Open University, UK	The use of the CaMV promoter incurs unique risks	Ho et al., 1999
	Ajay Kohli; John Innes Center, Norwich, UK	A recombination hotspot in CaMVcreates a variety of risks of recombination, with other genes and with other viruses	Kohli et al., 1999
	Siva Kumpatia, Texas A&M	Genomes have evolved diverse ways to distinguish self from non-self at the genomic level, and to excise or silence alien DNA	Kumpatia et al., 1998
	M. De Neve, University of Ghent, Belgium	Differences in gene silencing profiles among five homozygous lines of transgenic *Arabadopsis* led to the conclusion that "gene silencing phenomena could hamper the general economic exploitation of plants as production systems for heterologous proteins."	De Neve et al., 1999
	T. Demeke, University of Saskatchewan, Canada	Due to gene silencing, even when the transgenes themselves are stably inherited, the traits they encode may not segregate according to Mendelian ratios. Transgenic constructs can lose their effectiveness within as well as among generations	Demeke et al., 1999
Ecology	Miguel Altieri, University of California, Berkeley	Ecological risks from transgenic crops parallel those from pesticide-based agriculture	Altieri (in press)
Food science/ nutrition	Arpad Pusztai (ret.), Rowett Research Institute	GE potatoes with snowdrop lectin and the CaMV promoter affect rat intestines	Ewen and Pusztai, 1999
	Brian Fenton	Snowdrop lectin binds to human white cells; argues for greater care before incorporating plant lectins into GE foods	Fenton et al., 1999
	R. Schubbert, University of Kohn Germany	Alien DNA is not completely degraded to mononucleotides during digestion, and further, the intestines are not a barrier to the movement of recombinogenic DNA fragments.	Schubbert et al., 1997; Doerfler and Schubbert, 1998; Schubbert et al., 1998
	T. Inose	Inserting multiple copies of an existing gene in yeast elicited a 40- to 200-fold increase in methylglyoxal (MG) – a toxic and mutagenic substance	Inose and Murata, 1995

are safe for human consumption will have been shown to be mistaken. To prove that consumption of such products will never produce such harmful consequences for any group of humans would require research that is limitless in both cost and timeframe.

Proponents will maintain that they are not saying that GM crops are absolutely safe for human consumption; only that they are no more risky than unmodified crops. However, this response misses the point. Proving that GM and non-GM crops are equally safe is an equally sweeping gener-

alization. Research to support this conclusion would also require unlimited research resources.

Both proponents and opponents are aware that scientific proof of safety is a literal impossibility. Yet, proponents maintain that GM decisions should be made solely on the basis of scientific as opposed to ideological considerations. Rather than proving that GM crops are safe, government regulators try to come to a decision on rational grounds that we have sufficient scientific evidence to warrant accepting the conclusion that use of a product, whether it be a GM crop or a crop containing a pesticide residue, is safe enough.

However, and this is our second argument for the claim made above, the basis for this decision includes many normative assumptions as well as scientifically established factual claims. Reasonable people often differ amongst themselves regarding such normative matters. In regard to the acceptability of GM crops, proponents and opponents may differ in regard to how extensively research on safety should proceed prior to making the decision that a crop is safe enough or as safe as a non-GM counterpart. They may differ in regard to what sorts of scientific information are required to make this decision in a rational way.

Consider, for example, whether it is reasonable to say that a GM product is safe enough for human consumption based on short-term acute toxicity tests or whether long-term tests are needed to investigate chronic effects. Is testing of the single target protein coded for by the transgene predictive of risks from eating the whole food (see Part III)? Is one animal model (rats) predictive of effects on other species (including humans), or on other classes of animals such as on young animals, old animals, lactating animals, pregnant animals, or on the increasingly large immunocompromised segment of the population? As a contributor to the NAS committees that published *The Delaney Paradox: Regulating Pesticides in Food* (1987), and *Pesticides in the Diets of Infants and Children* (1993), Wargo (1996) demonstrated how basing pesticide risk assessments on healthy white males has compromised the health of infants, children, and other groups.

Thoughtful, intelligent people differ as to when or under what conditions it is ethical to expose people to risk of significant harm. The differences among such people are profound. Differing values lead people who accept the same scientific opinions as true to reach contradictory conclusions regarding the acceptability of use of the same product. However, differing values also make it difficult to achieve agreement as to what are the facts. These matters have been discussed at length in works of Brunk et al. (1991), Lehman (1995), Shrader-Frechette (1995a and b),

and Thompson (1987a and b; 1990a and b). Brunk et al. (1991), Lehman (1995), Rescher (1983), Shrader-Frechette (1985a and b), and Thompson (1987a and b; 1990a and b).

Suppose we are legislators or government regulators and we are considering whether to accept the use of a GM crop. We want to take into account both food safety and risk of harm to aspects of our environment. We want to make our decision in the most rational way possible, based on scientifically validated knowledge. However, particularly in the case of GM crops, we have to make the decision under considerable uncertainty. We do not have sufficient experience to determine an objective probability of harm or benefit. Regarding environmental risks of GM crops, for example, Gidding (1999) cited evidence that the invasiveness of a GM crop could not be modeled from, a) biological, genetic, and/or environmental traits, b) vegetative or reproductive traits, c) an annual or perennial growth habit, d) inbreeding or outcrossing, or e) level of polyploidy or heterozygosity. In terms of colonizing ability, she further noted that "differences between plants that succeed and fail are often apparently trivial ... and may be determined by just a few genes." How can we allege lack of environmental risk, in this case, of invasiveness, when our understanding of invasiveness is itself so illusive?

Further, we cannot look at a long run of cases in which the crop was used and determine the frequency with which specific harms or benefits resulted. At best, the crop may have been tested in a few cases under carefully monitored conditions, the results of which have not been subject to peer review or publication. The allegation that the safety of GM crops can be inferred from the history of safe use and production of unmodified crops rests entirely on the unvalidated premise of substantial equivalence (see Part III).

Given the unavoidable uncertainties and the differences in normative assumptions, proponents and opponents of the technology will almost certainly **not** appeal to the same set of facts in trying to come to a conclusion about the probability of harms and benefits. Assuming that proponents and opponents were each able to design and conduct the research that they thought would be most appropriate, it is likely that they would not conduct the research in the same way. They would make different decisions as to what circumstances were relevant for such a test. It is unlikely that educated proponents and opponents of the use of the new technology would agree as to the probabilities at issue.

Now you may suggest that the factual divergences between proponents and opponents could be resolved simply by doing further research. However, it is unlikely that they will reach agreement as to what research is

worth doing. Divergent value assumptions and associated beliefs will lead opponents and proponents to investigate distinct issues. As reported in the summary of the 10-year *The Global Environmental Change Programme* in the UK, "current approaches (to risk assessment) . . . fail to recognize that the underlying assumptions used at the start of the process of risk assessment affect the outcome" (Tansey, 2000). Even where they wish to investigate the same issues, their divergent values will lead them to make differing assumptions concerning the conditions under which these issues should be investigated.

Thus, it is reasonable to expect that differences in value assumptions will create divergences among the alleged factual bases for the study. Potential environmental harms may loom large in the minds of opponents of the technology, leading investigators to focus on effects on the soil (Saxena et al., 1999) or on beneficial insects (Hilbeck et al., 1998). Conversely, proponents of the technology would consider such issues of less importance. These propensities will influence the thinking of both proponents and opponents as to what research is required in order to reach a rational judgement about the acceptability of the technology.

When the research is concluded, opponents will weigh potential harms more heavily, while weighing alleged benefits more lightly. Opponents of the use of the technology will argue that the technology should not be regarded as safe enough if there is reputable scientific evidence that the technology causes harm. They will not necessarily demand strict scientific proof that the technology causes harm but will favor taking precautions on the basis of the evidence available until stronger scientific evidence can be obtained.

Conversely, proponents of the technology will attach more weight to the potential benefits of the use of the technology and less to the potential harms. They will argue that the technology is acceptable for use if it has not been scientifically proven to cause serious harm. Doing further research will not lead to resolution of these divergences in values. These matters have been pursued in considerably more detail in the work of Brunk and the others (above).

However, to focus on the pragmatic, let us ask how an ideal legislator or regulator would proceed in the circumstances we have outlined. An ideal legislator or regulator is one not predisposed to favor either the proponents or the opponents of the use of the technology. While such a person cannot hope to achieve agreement, she can hope to have the best possible research and reasoning presented by parties on each side of the issue. She can try to find the best researchers and the most acute risk analysts and give equal financial and other support so that good research and analysis can be done

by both opponents and proponents. Then, when all sides have presented their reports, the legislator or regulator can carefully sift the evidence and reasoning in the hopes of reaching a correct decision on the matter.

Of course, in the real world that is not how things happen. According to Rissler and Mellon (1996), as reinforced by Nader et al. (1999), GM crops currently in commerce have been subject to reviews that were "minimal, short-term and conducted by industry (and largely unpublished, rather than public and peer reviewed) and have not addressed the full range of the risks" posed by GM crops. Since much of the research is not peer reviewed (e.g., Table II), both the public and other scientists have less reason to trust the quality of the research than is typical for developments in agriculture.

As reported by Tansey (2000), *The Global Environmental Change Programme* concluded that current approaches to risk assessment are inherently flawed. Supporters of genetic engineering have appealed to inherently fallacious arguments in support of their view. They claim the safety of GM is reflected in the fact that millions of people have consumed GM products and no harmful effects of such consumption have been proven. For example, Trewavas (2000) stated that:

> The testing of GM food is exemplary in its detail and takes at least four years. Sir John Krebs, Head of our new Food Standards Agency concluded that GM food is as safe as its non-GM counterpart. If eating foreign DNA and protein is dangerous we have been doing so for all of our lives with no apparent effects.

Apart from the fact that only very young children could have been eating GM food all their lives, the weakness of this argument is revealed by noting that the manufacturers of cigarettes, or lead-based paint, or PCBs could and did make the same argument in support of their products just a few decades ago. Clearly, absence of proof that consuming GM crops causes harm is not itself proof that the products do not cause harm, particularly in the absence of targeted research. If such products do cause harm, but the food is unlabeled and hence inaccessible to epidemiological monitoring, and if no one is investigating that particular harm, then no proof of harm can be forthcoming.

PART III

Because of its pivotal role in risk assessment, the implications of *substantial equivalence* merit further consideration. The term *substantial equivalence* harks back to ideas found in the works of ancient and medieval thinkers. Saying that two foods are substantially equivalent suggests that their differences are unimportant so far as food safety is concerned. This

implication embodies a value judgement, although one that is obviously not shared by a growing number of consumers in Europe, Japan, North America, and elsewhere.

GM foods or food components are deemed to be safe for human consumption if they are substantially equivalent to the foods from which they are derived. Where a GM food is considered to be novel, or not similar to previously existing foods, as in the case of Myco-protein derived from a fungus as assessed in the UK, then it is deemed not substantially equivalent. This was the case with a protein product referred to as Myco-protein that was derived from fungi, as assessed in the United Kingdom. Of course, if other products are derived from the same fungi, the notion of substantial equivalence would be applicable in those cases because of the prior existence of Myco-protein (OECD, 1993).

Substantial equivalence has been explained as follows:

> . . . 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. (OECD, 1993)

Whatever this means, it clearly does not imply that two products that are deemed substantially equivalent are chemically or biologically identical. They cannot be, because by definition, the GM product has been endowed with patentable biological properties that are not found in its non-GM counterpart. Thus, when regulators say that product A is substantially equivalent to product B, what inference should be taken? Do they want us to believe that a GM product, such as Bt-corn bearing active endotoxin in every grain, does not affect the metabolism of humans, livestock, or non-target insects *differently* than unmodified corn? If this is what they mean, it is an unwarranted claim. Infinitesimally small differences can readily affect health – whether of humans, livestock, or wildlife. Consider the tragic case of L-tryptophan, a nutritional supplement that had been marketed by Showa Denko of Japan and other companies for many years. Shortly after switching to a GM-source (Strain V) for producing the L-tryptophan, a trace contaminant called EBT appeared in the product, killing 37 people and permanently disabling 1535 others. Although 99.6% pure, well within quality standards, the contaminant was still enough to kill and disable, forcing payment of billions of dollars in compensation from Showa Denko (Boyens, 1999).

The definition of *substantial equivalence* is sufficiently nebulous as to lead Millstone et al. (1999) to conclude that:

> . . . substantial equivalence is a pseudo-scientific concept because it is a commercial and political judgement masquerading as if it were a scientific one. . . . It is, moreover, inher-

ently anti-scientific because it was created primarily to provide an excuse for not requiring biochemical or toxicological tests.

Those challenging the critique of Millstone et al. (1999) (e.g., Kearns and Mayer, 1999; Trewavas and Leaver, 1999) cited the OECD (1993) document that posed the term substantial equivalence. However, the term has never been explicitly defined, either in the original OECD document or subsequently. Rather, the OECD (1993) document demonstrates how substantial equivalence pertains to specific cases.

For example, the GM yeast was tested after 100 generations and the hybridization patterns were unchanged, so the DNA of the GM yeast was considered to be genetically stable. Further, "the biochemical reactions occurring during the leavening process are the same in the genetically modified strain as in the unmodified strain." The authors therefore concluded that the two strains are substantially equivalent and therefore that it is unlikely that toxic metabolites will be produced in the genetically modified strain. It was further argued that because unmodified species of baker's yeast have been used historically in producing dough, without adverse effects, and because the genes are well "integrated into the chromosome," the GM yeast will not produce unexpected effects. It does not appear that this conclusion was tested experimentally.

The OECD (1993) concluded that another GM product, "low erucic acid rapeseed" was substantially equivalent because the composition of the oil was "comparable" to that of many other vegetable oils such as soy, corn, or peanut oil. They did not define the range of divergence allowed within the term "comparable." Considerable allowance for individual judgement appears to be given to the inference of substantial equivalence from composition products. No guidance is given as to how *different* the products could be, while still being substantially equivalent.

Also missing from current risk assessment protocols (e.g., Food Directorate, 1994) is the recognition that gene insertion affects not just the target trait, but also the stability of its expression, as well as the expression of other, wholly unrelated traits (Inose and Murata, 1995; Meyer, 1996; Andow and Hutchison, 1998; Kumpatia et al., 1998; Demeke et al., 1999; De Neve et al., 1999; Hansen, 1999; Brown, 2000). Even genes from the same species can elicit these types of unpredictable expression problems, as shown by Bergelson et al. (1998), who changed *Arabadopsis thaliana* from a selfing to an outcrossing species simply by inserting a gene for herbicide tolerance – a gene derived from naturally occurring mutant individuals of the same species.

A transgene can also elicit chemical and other differences – unrelated to the intended trait – between the GM and unmodified entity (Inose and

TABLE IV

Number of sites (of 4) showing statistically significant differences with the parental control, for each of 6 parameters, by CPB line (total of 4 × 6 = 24 contrasts for each line)

CPB line	Total solids	Dextrose	Sucrose	Vitamin C	Protein	Glyco-alkaloids	Total (% of 24)
1	2	0	0	1	1	0	4 (17%)
2	0	0	0	0	0	0	0
3	0	3	2	1	0	0	6 (25%)
4	1	2	0	1	0	0	4 (17%)
5	1	1	1	1	0	1	5 (20%)
Total	4 (20%)	6 (30%)	3 (15%)	4 (20%)	1 (5%)	1 (5%)	20 (17% of 120)

Murata, 1995). For example, one part of a GM submission to Canadian regulators (Ingratta, 1996) involved 5 lines of Colorado potato beetle (CPB) resistant potato (from cv. Atlantic) grown at four sites for one year, with six measured parameters (Table IV). Twelve to fifteen replicated plots were sown per line at each site, but only four plots per site (total of 16 measured plots per line) were analyzed. These results were accepted as evidence of substantial equivalence in nutritional composition. Differences between the CPB lines and the parental control ranged from nil for Line 2 to 25% for Line 3, yet all 5 lines were found to be substantially equivalent (Health Canada, 8 November 1996; FD/OFB-096-313-A[3]). Because all GM submissions to date, in both the US and Canada, have been found to be substantially equivalent, it is unclear how different something would have to be in order for it not to be found substantially equivalent.

In determining that a new product is substantially equivalent to an existing product, the goal is to determine whether there is reasonable certainty that the new product will not cause harm "from intended uses under expected conditions of consumption" (OECD, 1993). So far as we can determine, the notion of "reasonable certainty of no harm" is not defined. Does "reasonable certainty" imply that there are no reason-

[3] http://www.hc-sc.gc.ca/food-aliment/english/subjects/novel_foods_ and _ingredient/decisions1_1994.html and then click on the November 96 decision on Monsantos CPB potatoes.

able doubts about the possibility of harm? Alternatively, does "reasonable certainty" imply only that on balance the evidence suggests that the probability that the product will not cause harm is greater than 50%? In legal contexts, these two concepts of certainty are not equivalent. It is far easier to show that the probability that there will be no harm is greater than 50% then it is to show that there are no reasonable doubts.

As noted above in Part II, decisions regarding safety involve normative considerations about which reasonable people can disagree. However, because substantial equivalence does not require even experimental feeding trials of the GM crop (although such trials may have occurred for some crops), there is clearly room for disagreement concerning the level of certainty in the safety of GM crops for humans, livestock, and wildlife. People making the determination of substantial equivalence, and thereby, the safety of GM crops, are making judgements that necessarily reflect their own values rather than the depth of scientific understanding that one might have expected to underpin such an endeavor.

Despite its lack of scientific rigor, as emphasized by Millstone et al. (1999) and Brown (2000), substantial equivalence remains the pivotal lynchpin of the risk assessment process in Canada and the US. Once a GM crop has achieved this designation – as have all submitted GM crops – then no more specialized testing is required, and the crop is free to enter commerce. Indeed, approval grants the proprietor the right to use the GM crop itself as a parent to introduce transgenes into other lines of the same species without the need for resubmission, testing, or even notification prior to commercialization. The available evidence supports the conclusion of Millstone et al. (1999), that substantial equivalence is basically a vehicle to facilitate the commercialization of GM crops. A protocol that relies so profoundly on substantial equivalence, and which fails to exclude any submission, can hardly be credited as a tool for safeguarding either food safety or the environment. Given the manner in which GM food safety is tested, insufficient evidence is available to provide scientific warrant for claiming that products judged substantially equivalent will function safely or similarly in all human beings.

CONCLUSION

We summarize the claims we have supported as follows:

1. Allegedly factual claims offered in support of the view that we are proceeding too hastily in the production of GM crops are, in many instances, based on valid scientific arguments. Allegations that

opponents to the immediate deployment of GM crops are necessarily anti-science or practitioners of junk science are without foundation.

2. Claims that GM crops are safe for human consumption and for the environment have not been well validated by peer-reviewed research, and indeed, cannot be validated by science alone. The risk assessment process is science-based, but rests on controversial assumptions about which facts are relevant, and ultimately, on values about which reasonable people may disagree. In light of these assumptions, we are not entitled to claim to have knowledge, scientific or otherwise, that products are safe enough. At present, claims about GM food safety are educated guesses, and in some cases, the guesses are controversial. Demands for "science-based" decision-decision-making cannot be fulfilled at the present time, in part because of the virtual absence of relevant risk assessment research but also because of the lack of consensus on what *is* relevant research.
3. Despite its pivotal role in the commercialization of GM crops, substantial equivalence is poorly defined. In consequence, it is impossible to determine how different a GM crop would have to be to not be substantially equivalent to its non-GM counterpart. The conclusion that a GM food is substantially equivalent to a non-modified food, when applicable at all, is based on assumptions and value judgements that are not universally shared. Methods that have been used to determine substantial equivalence require neither observational nor experimental tests of either food safety or environmental risk.

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