ONE HUNDRED PERCENT SAFE?

GM foods in the UK

Collected and collated for CROPGEN

by

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1. SUMMARY

Don't fear failure so much that you refuse to try new things. The saddest summary of a life contains three descriptions: could have, might have, and should have. — Louis E. Boone

In all sorts of contexts, and in lots of conversations, it has become clear to us that many people, while often recognising the benefits of genetic technology in agriculture, feel uncomfortable about the safety of GM foods. Many are unaware of how much testing has actually been undertaken and of the enormous efforts both by the developing companies, and by the regulatory authorities, to ensure that these foods are as safe as their "conventional" counterparts, if not actually safer. It is primarily for them that this Report is written, so that they may look up for themselves just what it is that has been approved, why and by whom.

This Report therefore takes an overview of the regulatory procedures for GM foods. It summarises their findings and offers an interpretation of their significance to encourage people to make up their own minds about the safety of transgenic foods.

In **The meaning of "safe"** we ask just what is meant when we say that something — anything — is "safe". Safety appears always to be defined in terms of an absence of harm, danger or damage; such a definition inevitably limits an absolute assertion of safety for food or any other product or activity because we cannot know the future. In practice we extrapolate from past and present experience to make what we hope is a reasonable forecast of the future but it can never be more than that: forecasts may sometimes be wrong.

Some critics of GM food and its approval procedures argue that a more elaborate regulatory scrutiny is called for, akin to that for clinical drugs. We therefore take a look at **Approval procedures for clinical drugs** and ask how relevant — and how close —they are to the way in which novel foods are handled.

In **Testing novel foods** we move on to inquire more precisely what food testing generally entails and what would be required for pharmaceutical testing.

That leads to a discussion of **Substantial equivalence**, a important concept employed by all regulatory authorities as a basis for ***beginning*** an examination of novel foods but not accepted as adequate by some shades of opinion. However, substantial equivalence is not the whole story; the authorities are always able to demand more information if and when they think it appropriate, and to refuse approval until they have it.

Regulation and the regulators considers the underlying rules, actual processes and competent authorities involved in novel foods approvals.

Chapter 11 and the appendices detail the individual food properties and the approval decisions of the regulatory bodies for the GM **Foods approved for use in the UK.**

When **Evaluating the data**, we note the role of the regulatory authorities, compare the testing procedures for clinical drugs and novel foods, review hazards and risks, comment on

the views and statements of the critics of transgenic food technology, and adopt a view on the precautionary principle.

This leads to our **Conclusions**: that for all practical purposes, transgenic foods approved for UK use do indeed appear to be safe but that nobody can know the future and 100% certainty is not possible for anything.

CropGen mission

A consumer and media information initiative, CropGen's mission is to make the case for GM crops by helping to achieve a greater measure of realism and better balance in the UK public debate about crop biotechnology.

At the heart of CropGen is a panel of scientists and others who recognise that crop biotechnology offers many potential benefits — benefits which have been largely absent from the public debates to date.

While ultimately funded by industry, CropGen's panel members are free to express such views as they consider appropriate. The funding companies cannot veto the panel's position on any issue.

2. OBJECTIVES

Forgetting our objectives is the most frequent stupidity in which we indulge ourselves. — Friedrich Nietzsche

The purpose of this Report is to:

1. review the regulatory procedures for evaluating the health aspects of novel foods, including those from transgenic sources;
2. discuss some of the relevant issues and concepts;
3. refer to the evidence relating to health linked to the use of ingredients derived from the genetically modified crops which may presently be used as food sources in the UK;
4. note what the regulators have said about those foods approved for sale in the UK; and
5. to provide our own interpretation of what it all means for consumers.

We outline the regulatory procedures in force in this country and some others, recording where the evidence presented to the regulatory authorities or otherwise publicly released may be found. However, we cannot claim to have been exhaustive because there are so many items of information, often of minor value, that we may well have missed some of them or have decided they would extend this task unreasonably for little added value.

As we shall describe, we do not attempt except in a general sense to evaluate the primary information: that is for the specialists and we will be content to record their views in the form of regulatory decisions and draw our own conclusions from them. It is nevertheless important for consumers in general to know that much of the relevant information is in the public domain and where it may be obtained or consulted if they know where to look for it. We therefore aim to provide enough pointers to enable interested readers, if they so wish, to find the information and come to their own conclusions.

Some commentators of the biotechnology scene have drawn a comparison between the regulatory procedures for transgenic foods and those for clinical drugs produced by the pharmaceutical industry. Some, indeed, have called for full pharmaceutical testing of the new food products, subjecting them to the same tests as those for new drugs. It is therefore relevant for this Report to consider the reasons for the differences in regulatory procedures for pharmaceutical products compared with those for transgenic foods and to contrast the nature of the data available for general public scrutiny.

3. INTRODUCTION

With the introduction of agriculture mankind entered upon a long period of meanness, misery, and madness, from which they are only now being freed by the beneficent operation of the machine. — Bertrand Russell.

Attitudes towards the use of biotechnology in food and agriculture have become highly polarised, particularly in the UK and some other European countries. While GM crops are being rapidly developed ***and used*** over large areas of the Americas, Australia, Africa, Asia, and Eastern Europe, in Western Europe the arguments wax fast and furious about whether such methods should be applied to agriculture and food production.

As with all new technologies, there are fears of unknowable damage. Examples from history abound: the riots which took place with the introduction of vaccination for smallpox, the fear that railway trains would cause severe illness, as it was clearly unnatural to travel at 20 miles an hour, and the condemnation of pasteurisation as the end of healthy living were all major areas of contention when they were first introduced. In time, people became used to the new ways and they were eventually regarded as commonplace.

In 1996-7, the arrival in Europe of genetically modified (GM) crops, and particularly the foods derived from them, provoked a heated discussion both about their desirability, and their effects on human health and on “the environment”. By 1998, proponents and opponents were (and are) equally forceful in putting forward their views on all of these issues, often from quite different positions and with few if any points of contact between them.

Many of the ideas and concepts underlying the data we discuss in this Report, as well as some of the data itself, have recently been reviewed in the wider context of food safety issues in an excellent publication by Kuiper ***et al***. (1) which includes references to a number of papers published in peer-reviewed journals.

GENES, “NATURE” AND FOOD

There is not a choice between foods that contain genes and those that do not; all foods contain genes and while these are not species specific, they do exhibit minor variation between alleles. Although our common food plants exist nowhere in the wild, a major concern about GM crops is that they are somehow “unnatural” compared with other plants. The particular worry is that the transfer of genes “across species boundaries” might lead to health and other problems. Most molecular biologists, however, adopt a different view. A gene is primarily a piece of information contained in physical form as a section of DNA in a code that is common to all living organisms .

A gene present in a particular organism is not necessarily unique to it. Thus, humans share some 98% of their genes with chimpanzees, perhaps 95% with pigs and a fair proportion (maybe 30%) with tomatoes. That is because ultimately we all derive from common ancestors and carry that inheritance with us. We can "read" one another’s genes. It is rather like words in a language: a word might appear for the first time in a Shakespeare play but, once there, it can be put into any other piece of text where that meaning is needed. The fact that it started with Shakespeare does not invalidate its use elsewhere. And we may never know whether perhaps Shakespeare got it from somewhere else; words are currency, moving around to be

used when and where appropriate.

So it is with genes. The horror some people say they feel at the idea of transferring a gene coding for an "anti-freeze" protein from an Arctic flounder to a plant is misplaced: there is nothing magic or restrictive either about the gene itself or its location in the fish. Anti-freeze genes are already present in some plants and it becomes purely a matter of convenience and suitability which one is transferred to confer frost resistance to the recipient plant. We might well already have eaten the gene and its protein product in the fish; it would be unlikely to make any difference if we were to eat it in the transgenic plant.

Insect resistance is another case in point. The Bt gene used to render maize resistant to the European corn borer pest is derived from a bacterium which naturally carries it. Indeed, the bacteria making the toxin are widely used as an insecticide (in both conventional and organic farming) so we have been eating the protein in those spray residues for years on all manner of plant products. The gene is able to produce the Bt protein in the maize because genes often function similarly wherever they are found – an expression of the unity of biology.

"But this cannot happen in nature" is a common reaction and hence such gene transfers are sometimes seen as inherently "unnatural". There is growing evidence that horizontal gene transfer (i.e. the exchange of DNA between species) ***can and does*** occur in nature; some people feel it is the very stuff of evolution. Nature is a very big place and has been in action for a very long time. There has been plenty of time and space for all manner of gene transfers to have taken place. Many, probably most, of them would have conferred no advantage on the recipients and would have died out in the eternal scramble for survival. It is only in the relatively cosseted circumstances of agriculture than these new agricultural biotechnological hybrids enjoy an advantage; it is likely that they, too, would not survive in the wild. Indeed, recent studies at three sites in Britain have explored the fate of GM and conventional oilseed rape, maize, sugar beet and potato which were left untended and monitored over a period of 10 years: they had all died out after 3-5 years except for one site sown with ***conventional*** potatoes which still persisted after ten years (2).

There have been claims that there are specific hazards arising from GM foods which are distinct from those of non-GM foods bred by conventional methods. In her paper ***The Great Food Gamble***, Diamond (writing for Friends of the Earth) observed that "there is a possibility, as a result of GM, of significant alterations to the metabolism of GM food plants"…"and there is the fact that most novel proteins inserted into GM crops are entirely novel in the food chain" (3). These remarks, however, are unsupported assertions: conventional breeding has for millennia exchanged unknown numbers of genes with unexplored consequences, while many of those “novel” proteins already exist in food and the Bt toxin used in insecticide sprays will inevitably leave residues on the crop. Diamond concludes that the safety assessment, as it stands, is not able to identify every GM crop which might be harmful to human or animal health as it goes through the testing protocols but that does not seem to be what the world’s regulatory authorities think as we shall find later (4).

FACTS AND OPINIONS ABOUT GM FOOD SAFETY

Because all these matters are complex, none of them can easily be resolved by a simple or straightforward presentation of “facts”. There are just too many facts of supposed relevance and too much debate about what does and does not constitute a relevant fact. Although there is no shortage of data, it is rarely entirely clear and conclusive. Furthermore, for reasons of their own, some of the parties use and manipulate data to suit their individual purposes: information favourable to their own point of view is repeatedly (and often loudly) trumpeted while anything which does not support them is ignored. Even when specific “facts” are recognised by both sides, very different interpretations may be put upon them.

As we have noted, one of the major questions is whether or not there is or may be any impact on human health resulting from the consumption of foods or ingredients deriving from GM crops. The evidence for and against takes a number of forms:

1. a variety of tests and investigations performed by the applicants for approvals to market such products, usually undertaken by the companies producing the new materials although there have been cases of public sector institutions (universities or research institutes) making such applications. We shall be referring in some detail to applications for approval and their evaluation;
2. papers published in learned journals and elsewhere of variable quality and content. We shall note some papers of this sort. Typically they do not deal with all aspects of health matters for individual products but consider parts of the problem or take a wider view;
3. a few major reviews dealing with published material in some depth but not necessarily all reaching similar conclusions (5, 3);
4. the experience derived from the consumption of these foods by large numbers of people over a period of several years.

In addition, there have been very many opinion publications in which the authors, often without dealing in detail with primary research data, draw their own conclusions about the safety or otherwise of GM foods.

It is not our objective to review the whole of this literature: much of it is repetitive and, often not offering hard facts, does not allow an independent observer to draw his own conclusions. Rather, we have concentrated mainly on applications and supporting documents provided to regulatory authorities together with the responses of such authorities to the applications submitted to them. In some countries the data is open for public inspection and members of the public actually participate in the regulatory process.

It is sometimes claimed that because data on the health safety aspects of GM foods have not been published in peer-reviewed journals, they are ***ipso facto*** unreliable. That seems to us to be unreasonable. Unless one were to have an acute interest in the matter, the vast amounts of information submitted in support of regulatory applications would hardly make for fascinating reading so it is not surprising that it is not published in the normal scientific literature; furthermore, some of the evidence may be commercially sensitive. A number of critics therefore claim that it has not been subjected to peer review. We submit, however, that the material has in fact been peer-reviewed by experts as part of the regulatory process, experts with a duty to protect the public from dangerous, harmful or unhealthy novel foods. Although we are unlikely to know the identities of peer reviewers had the material been submitted to learned journals, we do know who the reviewers are for most

regulatory agencies since those organisations are very transparent, publishing full details of their membership (selected specifically for competence in the relevant area), often on their websites. Furthermore, in today's litigious society, it is not in any company's interest to skimp on safety evaluations. We therefore cannot conclude that peer review by a learned journal would be more authoritative than scrutiny by a regulatory authority. Nevertheless, much of the safety evidence actually has been published in conventionally peer-reviewed journals (1).

Having been through the regulatory approval process, we must also continue to monitor the consumption of GM foods by real living people. Since the widespread introduction of GM varieties into commodity food crops (particularly maize, oilseed rape and soybeans) and cotton, their use, above all in North America, has grown by leaps and bounds. Estimates suggest that in 2001, 68% of soybeans and about one-third of the maize grown in North America comprised GM varieties; these crops were, of course, also extensively grown in other countries. In North America, there is no mandatory requirement to label ingredients as coming from GM crops yet they have widespread use in processed foods from breads and breakfast cereals through ice cream and chocolate to baked goods, pies and a host of other products. For five or six years some 300 million people have willy-nilly been consuming GM food ingredients. Looking at what has happened ***and not happened*** to them hardly constitutes a controlled experiment but it does provide actual information.

As yet there have been no reports of any health effects to people who have eaten these foods. Of course, there can be a variety of explanations for an absence of reports, the most obvious ones being that nothing happened, that certain health effects may not have been recognised as deriving from GM foods and that, if you don't look for specific effects, you don't find them. In any situation as complicated as that of human health, it is impossible to test for every eventuality in advance and in any new situation there could be unknown factors which may or may not emerge with use. Friends of the Earth made that point in ***The Great Food Gamble*** (3). Commenting on the fact that no health effects have been found, the authors observed:

> ***One of the most serious failings of the current approach is that simple composition analysis is unlikely to detect unexpected or unintended impacts of genetic modification. In most cases, analysis of this sort relies on knowing what to look for. Obviously, an examination that focuses only on known substances will not reveal unknown substances that may have toxicological relevance.***

Nevertheless, neither can the absence of reported effects of human health be ignored. As an American newspaper put it (6):

> ***Three federal agencies are charged with ensuring the safety of biotechnology foods and crops: the Food and Drug Administration, the Department of Agriculture and the Environmental Protection Agency.***
>
> ***Meanwhile, the safety of biotech foods has been attested by such authoritative bodies as the American Medical Association, the National Research Council, the United Nations Food and Agriculture Organization and the World Health Organization. Former Commerce undersecretary for trade***

> ***David Aaron put it best last year when he declared, "Thirteen years of experience with biotech products in the U.S. have shown us that biotech foods developed and used in the U.S. present no safety risk beyond those of their 'natural' counterparts. "Not a single ailment has been attributed to biotech foods. Not one. Not a sneeze, not a rash, not a headache."***

Perhaps the clearest public statement came with Sir John Krebs' (now head of the UK's Food Standards Agency) call at the OECD Biosafety Conference in Edinburgh (March 2000) for anybody who was aware of the existence of any damaging effects of GM foods on human health to say so there and then. He was not asking at that point for details; he simply wanted to find out whether anybody in the hall actually knew of anything. His invitation went unanswered, the presence of representatives from Greenpeace, Friends of the Earth, the Soil Association and The Natural Law Party notwithstanding.

"An absence of evidence", some people say, "is not the same as evidence of absence". That sounds like a pithy comment but, as we shall find later, it is not so simple. Nobody has yet found a way of providing evidence of absence except as a consequence of an absence of evidence. Think about that: we shall come back to it when we discuss the meaning of "safe".

AGRICULTURAL BIOTECHNOLOGY AND GM FOODS

This is not the place to explain ***ab initio*** what genetic engineering is, how it is applied to plants to make new strains, why such strains may or may not be useful, what the probable benefits and possible hazards may be, nor how real are those benefits and how likely the hazards. Excellent accounts of all these matters and many others are readily accessible from a range of sources (7-12). Ultimately, such an understanding may indeed be essential for the proper and full analysis of health-related data. However, we assume here that our readers are either reasonably well informed or else do not wish to enter in great depth into such technological explorations, rather preferring to savour the tenor of the evidence without too much detail.

4. SOURCES

Variety's the source of joy below. — John Gay

All information and conclusions noted in this Report are in the public domain; in each case the access route is referenced.

We have been offered no private documents but in one or two cases we explained to the sources of some items that, while they may notionally be public, in effect they were very difficult to find and that an easier route was essential. Such routes were subsequently provided in every case.

Many of our references are to websites since these are so easy to access. They are not, of course, permanent sources and individual websites or web pages may be withdrawn or modified with or without notice, all clearly beyond our control. At the time we obtained each item of website information it was indeed there but we cannot promise that it has remained in place.

5. THE MEANING OF “SAFE”

You shouldn’t say it is not good. You should say you do not like it; and then, you know, you’re perfectly safe. — James Abbot McNeill Whistler

Before we go any further, we should make quite clear what we are writing about and what we seek to explore.

In recent years, there has been a widespread increase in the public demand for “safety” for every product and for every service — except, of course, those patently dangerous ones in which we as individuals choose to indulge. We need reassurance that no dangers are attendant and are often insistent on knowing on whom to place the blame if something does go wrong, and hence whom to sue for damages.

All the dictionaries we have consulted define “safe” and “safety” in negative terms, an absence of harm or danger. Since we cannot know the future, it is, of course, impossible to claim total safety for all time for anything. The best one can say is that thus far the product or service appears not to cause harm or constitute a danger, but tomorrow.....who knows? We read that travel by train is “safer” per mile than going by car; this means that there is less likelihood of harm befalling the traveller, not that there is no possibility whatsoever of danger as we know only too well from a series of recent accidents. Often we extrapolate our sense of safety from something we already know to the new product or service; comparison of the familiar with the unfamiliar is an important part of our evaluation.

Because “safe” and “safety” are defined negatively, absolute safety cannot formally be proven: “100% safe” is not a description than can be applied to anything at all. The best we can do is to extrapolate from what we do know of past performance to conclude that a product or service is likely to be safe (i.e. not to cause harm) in the future but there is not much point in trying to put a percentage number to it*. If we have been doing something without mishap for centuries, it seems likely that we can continue to do so but many of our activities are much more recent in origin and it is also true that by no means all of the traditional ones are free from danger. Walking seems safe enough but pedestrians are run over by errant vehicles or walk into something, or over the edge of something, perhaps with very grievous consequences.

It is therefore futile to claim, as critics of new technologies sometimes do, that “an absence of evidence (for harm) is not evidence of absence”. They are wrong. Since we can judge present and future safety only on the basis of past experience, an absence of evidence of

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*While hardly a rigorous estimate, a calculation might actually look something like this: 300 million people in the US and Canada have been eating GM foods for about six years. Maize and soybeans are commodity crops which, in North America, are not separated into GM and GM-free batches so that products made with either are likely to contain GM ingredients: soybeans are present in about 60% of processed foods with maize common in breakfast foods and some others. Suppose 90% of North Americans do not seek to avoid GM products and, on average, eat GM foods in some form, say, five times a day. In six years they would collectively have consumed 300,000,000 x 0.9 x 5 x 365 x 6 = 3 trillion foods containing transgenic ingredients. As no ill effects have been reported, their frequency must be less than 1 event in 3 trillion; that could be interpreted as those foods being more than 99.9999999999% safe — but not 100%.

harm is precisely the only evidence we can ever expect to accumulate for the absence of harm.

So it is with eating and drinking. Most of the food we traditionally consume is generally regarded as being safe and so free from harm: ***generally***, perhaps, but by no means always. We think we know from experience that high-cholesterol foods are harmful in the long-term because of the damage they do — or may do — to our cardiovascular systems. We also know that many foods cause allergic reactions in some people, some of them serious enough to be lethal. If such foods were now about to be offered for sale for the first time and had to pass the current regulatory procedures for novel foods, would peanuts, eggs, milk products, wheat products, strawberries and other fruits, as well as fish and shellfish, be permitted?

Furthermore, there have in the past been a number of accidents in which new cross-breeds of plants, obtained by totally conventional procedures, have caused poisoning, disability and even death among some consumers or field workers because of an unexpected presence of toxins. Needless to say, as soon as the faults had been recognised, the products were withdrawn but who would have expected conventionally-bred potatoes (13, 14), squash and zucchini (15) or celery (16, 17) to do that? In contrast, GM foods are tested for possible toxic effects.

All the evaluations of GM foods must therefore be understood in the light of the real meaning of food safety: that a “safe” food is one which, as far as we know and with the exception of specific individuals who may be peculiarly sensitive (e.g. peanut allergy), when consumed in moderation over a period of time does not result in identifiable harm to the consumer. There are uncertainties even in that cautious statement: “as far as we know”, “in moderation”, “over periods of time” and “identifiable harm” are all capable of interpretation but it is, perhaps, the best we might hope for.

6. KIWI FRUIT: A NOVEL FOOD?

The tree is known by his fruit. — Matthew xii. 33.

One of the last “novel foods” to be introduced into the UK before the current novel food regulations took effect was Kiwi fruit, first sold in this country in the late 1960s or early 1970s. It was novel in the UK context in two senses: it was a new import here, although it had been eaten elsewhere, and the Kiwi fruit itself was a development from its original source. It had never been tested anywhere to see if it was safe for us to eat. Nor, as far as we know, has it been tested since. We are not claiming it is dangerous (we do not know that), just that it has not been tested.

Kiwi fruit (the “Chinese gooseberry”) is native to China but does not figure prominently in Chinese cuisine. In the early 1900s, New Zealand growers produced a larger, less fuzzy variety which is the fruit known today. There are several varieties: one of them is a ***hardy Kiwi*** grown and marketed in Oregon as “baby kiwi”; it is called “Ananasnaya” or sometimes “Anna” because of its development in Russia about 60 years ago, with an uncertain parentage thought to be a combination of two species, ***Actinidia arguta*** and ***Actinidia kolomikta***, presumably with genes “crossing species boundaries”***.*** A number of crosses and varieties of Kiwi fruit are cultivated; we have no evidence that any of them have ever been tested for food safety.

Is it safe? Do we know? A recent report from Southampton General Hospital warned that a growing number of people are proving allergic to Kiwi fruit. Children as young as three months are showing adverse reactions to the fruit, which has become a common weaning food. Only one newspaper was interested in the fact that perhaps this fruit had not been sufficiently tested before introduction (18).

7. APPROVAL PROCEDURES FOR CLINICAL DRUGS

He gains everyone's approval who mixes the pleasant with the useful. — Horace

A possible comparison for the testing of transgenic foods is with that of clinical drugs. There is an extremely complex and elaborate procedure for making sure such drugs are effective and "safe", so much so that developing a new drug and bringing it to market is likely to take ten years and to cost hundreds of millions of pounds. It is not very different for GM crops: the cost of development and safety evaluation can also rise to many millions of pounds.

Some critics of transgenic foods maintain that the parallels between them and clinical drugs are so close that transgenic foods should also undergo clinical testing. Whether or not that is relevant and practical we discuss elsewhere and, in order to provide a framework for the comparison, it is appropriate to take a brief look at the procedures of clinical testing.

In the European Union, drug approval procedures involve both national authorities and the European Community. The Medicines Control Agency (MCA) under the Department of Health is the controlling body in the UK for clinical drug approval, evaluating safety, quality and efficacy. Proposed clinical trials must be submitted to the MCA and approved by an ethics committee (of which there are local and regional examples) to decide whether or not the trial as a whole should go ahead; there is also a Central Office of Regional Ethics Committees.

The Clinical Trials Directive of the EU aims for European harmonisation of the requirements for conducting trials in EU member states.

Regulatory procedures start as soon as a drug is introduced into animals (or humans) and is carried on post-launch throughout the life of the drug. Clinical trials, for which an application must be submitted with all relevant details, represents one of the periods of greatest activity in the regulatory process.

At each stage of drug development, the information required for approval is precisely stipulated, with the applicants encouraged to follow the published guidelines and formats (19 for the MCA rules, 20 for those of the European Union); if the guidelines are not followed, scientifically justified reasons must be given.

An Animal Licence is required for animal trials; the application must incorporate the design and experimental details of the trial as laid down in publicly available guidelines. These details and results are not available to the public. Clinical trials may be run in parallel with animal trials. On average, 4-5 years after a trial begins, the data are submitted to the regulatory authorities for approval; information relating to specific clinical trials is not released to the public unless the applicant company chooses to do so.

There are two possible routes to European approval:

Mutual recognition procedure: approval for the drug is first sought in one member state, e.g. the UK. As part of this approval procedure, the MCA assessors (permanent technical staff and civil servants) make their decision on the basis of information submitted by the applicant and on the advice of the Committee for the Safety of Medicines (CSM — whose

members are professionals, not civil servants, and who must declare any relevant personal interests). The CSM undertakes both a technical evaluation and a risk/benefit analysis for all new chemical entities in the UK.

The applicant may then inform the MCA of his desire to market in other EU countries and ask the MCA to obtain the necessary approvals. The MCA prepares a summary of its decision for the other Member States which, within a stipulated period (90 days), may accept the approval or alternatively may refuse it on public health grounds. The list of approvals is published on the MCA website, but without disclosing the basis of the assessments. For commercial reasons, the applicants normally do not publish details of the application themselves; members of the public cannot therefore find out for themselves the grounds for the approvals.

Note that the new UK Freedom of Information Act may affect the future release of information. The MCA is one of five government bodies undertaking a pilot study of what the implications of the Act might be (21). Recent reports, however, suggest the implementation of this Act may be delayed by several years

Centralised procedure: the body involved is the European Agency for the Evaluation of Medicinal Products (EMEA), an EU institution similar the UK's MCA. Applicants may apply directly to the EMEA if various requirements are fulfilled ***and are obliged to do so for approvals relating to "biotechnology" products"****. The EMEA reports to the European Community and, in so doing, generates a preliminary opinion as a basis for a decision on the application by the Commission.

The approval is published as a public assessment report: the ***Committee for Proprietary Medicinal Products European Public Assessment Report (EPAR)*** for ***BONIVA (International Non-proprietary name: Ibandronic acid)***, dated 25 June 1996, may be a typical example. The report's rubric states:

> ***"The European Public Assessment Report (EPAR) reflects the scientific conclusion reached by the Committee for Proprietary Medical Products (CPMP) at the end of the centralised evaluation process and provides a summary of the grounds for the CPMP Opinion in favour of granting a marketing authorisation for a specific medicinal product. It is made available by the EMEA for information to the public, after deletion of commercially confidential information…."***

The BONIVA document is sub-divided into the following sections:

(i) package leaflet: proposed information for the user;
(ii) summary of product characteristics: information for medical practitioners;

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*defined thus:

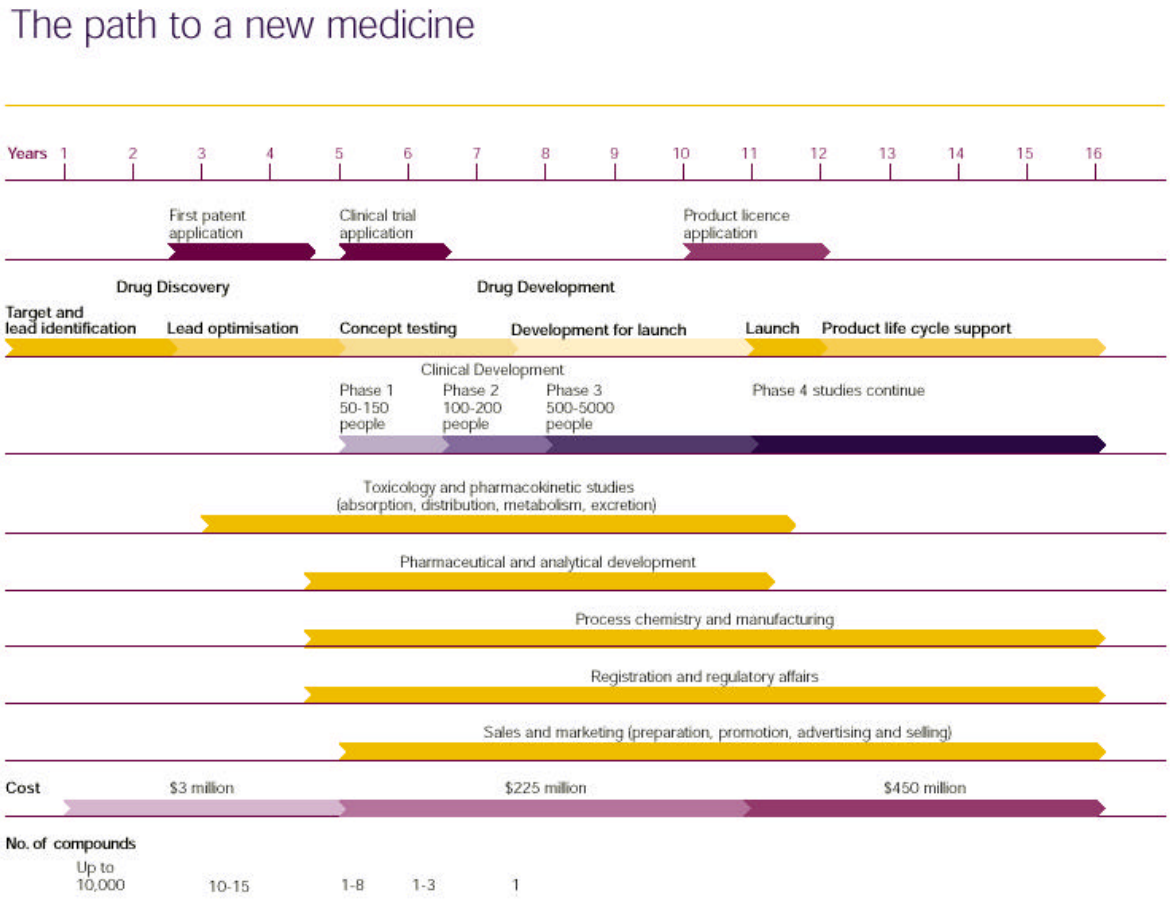
"Medicinal products developed by means of one of the following biotechnological processes:
recombinant DNA technology,
controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
hybridoma and monoclonal antibodies".

(iii) labelling;
(iv)scientific discussion comprising:

1. introduction
2. chemical, pharmaceutical and biological aspects (dosage form, method of preparation, staring material, control of the finished product)
3. toxico-pharmacological aspects (pharmacodynamics, pharmacokinetics and toxicology — the results are briefly summarised in the text but no experimental data are offered)
4. clinical aspects (pharmacodynamics/pharmacokinetics, therapeutic efficiency, safety and overall conclusions: limited experimental results and a summary of conclusions are offered but without experimental design details)

(v) brief review of the regulatory history of the product.

Developing a new medicine requires a major commitment of time and resource as the following diagram shows (22). The path from discovery of a potentially effective medicine to its launch on the market — and keeping it there — is a lengthy and complex process, and can cost some $450 million. The diagram shows the AstraZeneca process for drug discovery, development, commercialisation and launch. It uses a new terminology for the stages of development: pre-clinical (i.e. animal testing) prior to candidate drug (CD) nomination; concept testing, from CD nomination through to phase 1 and phase 2 completion; and development for launch, phase 3a and 3b activities conducted prior to filing. As the diagram shows, only a tiny number of starting compounds actually travel the full length of this path and a key element of successful research and development is the selection of substances which show the greatest potential to become significant advances in healthcare.



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8. TESTING NOVEL FOODS

Sweet food of sweetly uttered knowledge. — Sir Philip Sidney

The regulation of novel foods was introduced in the UK in about 1973; before then, new foods did not have to undergo the regulatory scrutiny which is now required and which has been applied to all novel foods including those from transgenic sources; novel foods are defined in the EU by directive EC 258/97 (42). Where does that leave us with regard to the food we now eat?

Foods offered for sale to the public do, of course, have to meet certain stringent standards of safety (i.e. freedom from harmful effects). Harm is likely to result mostly from decay or contamination with micro-organisms which might cause food poisoning: the presence of ***Salmonella*** in chickens, or of ***Escherichia coli 0157*** in prepared meats, are well-known examples of what can go wrong. But these are harmful effects ***not of the foods themselves*** but of contaminants; the foods ***as foods*** have to meet no regulatory requirements.

Although historically we have learned that foods sometimes need to be treated before consumption (removing toxins by peeling green potatoes and cooking beans), we have been eating eggs, milk products, bread, meat, fish, nuts and fruits from time immemorial without actually knowing whether or not they are harmful because nobody has ever tested them to find out. The best that has been done is, in some cases, to attempt to compare the health records of people who, for one reason or another, refrain from one or more of these foods with groups of people who do eat them. The trouble, of course, is that the two such sets of diets are never identical except for the one component under test; thus, their data can never be properly controlled and authoritative, but mainly give an impression. Even so, there are results which tell us that all the foods listed at the beginning of this paragraph are in at least some senses harmful (i.e. not “safe”): they may result in allergic responses or other types of food intolerance, or they may have long-term effects on our arteries and veins; some plant products we take into our systems are believed over time to cause cancer, tobacco being an obvious example. None of them is regulated for safety.

Transgenic foods, on the other hand, are “novel” and must be tested: can a proper trial be run akin to a clinical trial for a pharmaceutical drug? What might it take to do so? The agencies polling public opinion use a sample of 1,000 individuals or so to obtain a fair and proper cross-section of the national population. Presumably they exclude children under 18 as non-voters so, for food testing purposes, we might need about 1,350 people: although children have no votes, they do have bodies which might react towards certain foods.

We would therefore need two sample populations, one to eat the novel food, the other subsisting on a diet identical in every respect except that the novel food is replaced by the same food from a conventional source: say GM-maize on the one hand and conventionally-grown maize on the other. Never mind that the people in each group will certainly not have the same dietary tastes or preferences, they would all have to eat and drink exactly the same things. It would not be easy.

For how long must this test go on? A day, a week, even a year? That hardly seems very long when some people are worried about what might happen in ten years, or twenty or fifty;

“after all”, they say, “it takes that long for lung cancer to develop in smokers — and perhaps also for new variant CJD — and it might also take that long for something nasty to turn up with a transgenic food”. They might be right but we cannot see how such a test could be run:

1. it would be quite impossible to assemble the participants for the period and with the rigour required;
2. it would cost an unbelievable amount of money;
3. nobody would be remotely interested in developing products that required anything like such a degree of testing.

Nor is this all. Individuals may react differently according to their own genetic make-up: for example, they may show food intolerances or allergies. So, in addition to all the complexity we have just discussed, we would also need to know a good deal about the genetic characteristics of the people participating in the test.

The way of dealing with this aspect of evaluation is to run model systems to assess potential hazards: simple practical and rigorous procedures, perhaps similar to pesticide appraisal, but inevitably less complete. In applying for approval to market a transgenic food, the applicants undertake the tests prescribed by the regulatory authority who may ask for more information if they are not satisfied — and refuse to approve the new food until they get it. Continued monitoring after the product is on sale is a further check on effects. But exhaustive testing of the type described above for clinical drugs is simply not possible nor, indeed, would most people think it necessary. Many argue that because transgenic foods are so similar to the “conventional” foods from which they came, we need to concentrate the testing on the differences between them because we already believe the original to be “generally regarded as safe”. That leads us to the concept of ***substantial equivalence***.

9. SUBSTANTIAL EQUIVALENCE

If it looks like a duck, tastes like a duck and quacks like a duck, it probably is a duck. "No", says the sceptic; "it might be a chicken."

Substantial equivalence is an internationally recognised standard that measures whether a biotech. food or crop shares similar health and nutritional characteristics with its conventional counterpart. Biotechnological foods that are substantially equivalent have been determined to be as safe as their conventional counterparts. Products that are not substantially equivalent may still be safe but must undergo a broader range of tests before they can be marketed (23).

The concept stems from the report of a working group of national experts set up by the Organisation for Economic Cooperation and Development (OECD) to review the safety implications of modern food biotechnology. They considered numerous examples of how the safety of novel foods and food components had been evaluated in the past and established some guidelines and principles that underpin the safety evaluation of foods derived by modern biotechnology, principles widely accepted and similar to recommendations made by other influential groups, the World Health Organisation, and the Food and Agriculture Organisation (FAO) of the United Nations.

The report concluded that the most practical method to establish food safety was to ask whether a novel food (or food component) was substantially equivalent to an analogous conventional food product, where one existed. Account had to be taken of the processing (such as cooking) that the food may undergo, as well as how much food was to be consumed and by whom, and the dietary pattern.

In demonstrating substantial equivalence, it is important to take into account:

1. the characteristics and composition of the conventional food with which the new one is to be compared;
2. knowledge of the component parts of the new product or organism: any introduced genes, the method used to introduce the new genetic material and how that new genetic material is expressed; and
3. the characteristics and composition of the new product or organism compared with the existing food or food component.

If the novel food is judged to be substantially equivalent to an existing food, further safety or nutritional concerns are expected to be insignificant. Such foods are then treated in the same manner as their conventional counterparts. However, where new ***classes*** of foods or food components are introduced it is more difficult to apply the concept of substantial equivalence. Here experience gained in the evaluation of similar materials is taken into account. Where a product is thought not to be substantially equivalent to an existing one, further investigations, focusing on the identified differences are required. Totally new foods, where no similar materials have ever been consumed, must be evaluated solely on the basis of their own composition and properties (24).

The concept was endorsed by the FAO (25):

1. Food safety considerations regarding organisms produced by techniques that change the

heritable traits of an organism, such as rDNA) technology (i.e. “recombinant DNA technology”, often called “genetic engineering”), are basically of the same nature as those that might arise from other ways of altering the genome of an organism, such as conventional breeding.

2. Application of the concept of substantial equivalence is a basic tool in the assessment used to establish the safety of food products derived from genetically modified organisms. It is not a safety assessment in itself but is a dynamic, analytical exercise in the assessment of the safety of a new food or food component relative to an existing food/component.
3. The reference characteristics for substantial equivalence comparison need to be flexible and will change over time in accordance with changing needs of processors and consumers and with experience gained.
4. Substantial equivalence is established by a demonstration that the characteristics assessed for the genetically modified organism, or the specific food product derived therefrom, are equivalent to the same characteristics of the conventional comparator (conventional foods or food components already available in the food supply), within the natural variation for such characteristics, based upon an appropriate analysis of data.
5. The determination of substantial equivalence entails a consideration of the molecular characterisation of the genetically modified organism, its phenotypic characteristics and the key nutrients and toxicants for the food source in question. Analysing a broader spectrum of components is in general unnecessary but should be considered if there is an indication from other traits that there may be an unintended effect of the genetic modification.
6. While there may be limitations to the application of the substantial equivalence approach to safety assessment, this approach provides equal or increased assurance of the safety of food products derived from genetically modified organisms as compared to foods or food components derived by conventional methods.
7. When substantial equivalence is established for an organism or food product, the food is regarded to be as safe as its conventional counterpart and no further safety consideration is needed.

On the other hand, the concept has many critics. Their views are typified by the following statement by Millstone, Bruner and Mayer (26):

> ***“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 characterised 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."

Can we make sense of these arguments?

RECOGNISING THE THINGS WE KNOW

In our everyday activities, we recognise things we know because we have already come across in our lives and have some experience by which to evaluate them. Think of buying a new car. We have met cars before: we have an idea why they usually have four road wheels (one more-or-less at each corner), seats, an engine, brakes and all the rest. Most people have already owned or driven a car so they know generally what they are like. What interests them about a new car is mainly how it differs from the ones they have driven earlier: does it look attractive, does it have better brakes, more comfortable seats, a larger boot? They are applying the concept of substantial equivalence and then going on to explore and evaluate the novelties. We use a similar approach whatever we buy.

Every now and again we have the opportunity to buy something more unusual. Forty years ago it might have been one of the early photocopiers. Then we would have had to ask more questions because we might never before have seen a photocopier: what does it do?, how does it do it?, is it easy (and safe) to use?, does it use special paper?, does it require a particular ink?, will the operators get their fingers inky?; on and on, more and more questions until we get the hang of it. But now if we want a new photocopier we know exactly what to look for: how much does it cost to buy or to lease, and how much to run?

SUBSTANTIAL EQUIVALENCE AND NOVEL FOODS

The same procedure holds for novel foods. Think about Bt-maize, a maize plant with a gene from a bacterium added to the plant's own genetic material in order to confer resistance to insect attack. Maize plants without the new bacterial gene already contain tens of thousands of their own (plant) genes in each of their cells. Adding the insect resistance property introduces one new gene (plus the controlling gene switches). ***Substantially*** the new resistant plant is like the original: it looks like maize, grows like maize and tastes like maize — so is it maize? Overwhelmingly, of course, it is but it has been changed, be it by ever so little, and that change might have significant effects on the new plant. It might grow badly or produce small ears of corn, in which case it would not have been worthwhile developing commercially and we would have heard the last of it. Suppose none of those happened: as far as the grower or the consumer are concerned, the new plant is just like the old one except that it is less susceptible to insect attack, a property helpful for the farmer and good for the environment since less insecticide is used. But consumers want to know whether there are any disadvantages for them: perhaps the insecticide protein is poisonous, or allergenic, or maybe it causes other changes in the plant, which might make it harmful.

An obligation is therefore placed on the producer of the new variety to show that it is not harmful to consumers. We think we know that the maize ***per se*** is safe enough but what

about the new protein? That will already have been tested individually to see if it is acceptable. What if it has a secondary effect on the plant resulting in some other undesirable property, perhaps an increased expression of a poison or toxin? That possibility will also have been tested for. And we do need to keep in mind that, in the transgenic foods currently approved for UK use, only one digestible protein has been added in each case.

So far so good, but suppose a harmful effect is too subtle to be obvious or were not to show up as a health problem for decades? That is a risk which has to be taken. Think back to the new car. If a defect in its design or manufacture meant that its wheels might fall off after 100,000 miles there would be no way of knowing except for the car to be driven for that distance. Even that might be of dubious value: only some individual cars might have wheels which fall off and the distance might actually turn out to be 101,000 miles, not 100,000. It all comes back to not being able to know the future but only to be in a position to make some reasonable forecasts on the basis of past experience. When first encountered as new, would such a car have been considered as safe as other cars?

Similar arguments apply to food. If over several years, and through extensive testing and examination, that maize with an insecticide gene looks, tastes and behaves in every way except for its insect resistance like the maize from which it originated, one might reasonably conclude that it is no more harmful. Nevertheless, the harm could show up just a month later, like the wheels coming off after 101,000 miles. Nothing in life is or ever can be totally safe. One eliminates all the possibilities for harm that can be imagined and reasonably tested for but beyond that things are as always unpredictable and so one has to weigh up possible risk against perceived benefit.

One final point. The maize with which the insect-resistant variety is compared has, of course, not itself ever been tested: it is simply “generally regarded as safe”. So even if, after eating insect-resistant maize for fifty years, someone were to fall ill with an intestinal or other complaint, could we say that never before had a maize eater contracted such an illness after fifty years of eating maize and the illness therefore resulted from the transgenic manipulation? Doubtful.

10. REGULATION AND THE REGULATORS

Government is a trust, and the officers of the government are trustees; and both the trust and the trustees are created for the benefit of the people. — Henry Clay

IN THE BEGINNING

Transgenic bacteria, the first category of genetically modified organisms, made their appearance in the mid 1970s when biochemical knowledge had developed far enough for molecular biologists to understand how such manipulations could be done. As soon as the facts became known to the research community, scientists began to consider the wider implications of the new developments. It required no intervention by pressure groups; then as now, the scientists together with the regulatory authorities were and are well aware of the implications of their work, and the need for careful control to ensure that society reaps benefits not catastrophes.

In the summer of 1971, experiments were planned to introduce DNA from the SV40 virus into cells of the bacterium ***Escherichia coli***, a normal resident of human and animal intestines, and a favourite for laboratory use. This was of concern because SV40 is a monkey virus that can transform monkey as well as human cell lines into a cancerous state. The experiments were postponed.

In June 1973, a conference was held to discuss the safety issues of recombinant DNA as it related to laboratory workers. The US National Institute of Health (NIH) and National Institute of Medicine were asked to appoint a committee to study the matter. At the same time, letters were sent by notable scientists to the journals ***Science*** and ***Nature*** calling for a temporary halt to recombinant DNA experiments. Such a request was unheard of in the history of science. A Recombinant DNA Advisory Committee was established by the NIH at the behest of the scientists.

In February 1975, the Asilomar Conference was held on the Monterey Peninsula in California to discuss the relevant issues. The conclusion of that scientific conference was that most recombinant DNA work should continue but appropriate safeguards in the form of physical and biological containment procedures needed to be put in place (27).

It was from these beginnings that the current regulatory frameworks and procedures were developed, first in the US (where the technology began) and then, along roughly similar lines, in other developed countries.

Although the regulations governing novel foods in Britain derive from UK and EU legislation, the products now approved for use in the EU (and hence in the UK) were first introduced in the US. It is therefore relevant to note a number of points about the American regulatory system.

THE INTERNATIONAL CONSENSUS

Kuiper ***et al***. (1) discuss in considerable detail the thinking underlying the current concepts of food safety testing. They make a number of important points:

1. international consensus has been reached on the principles regarding evaluation of the food safety of genetically modified plants;
2. the concept of substantial equivalence has been developed as part of a safety evaluation framework, founded on the idea that existing foods can serve as a basis for comparing the properties of genetically modified foods with the appropriate counterpart. Application of the concept is not a safety assessment ***per se*** but helps to identify similarities and differences between existing food and the new product which are then subject to further toxicological investigation. No alternative, equally robust strategy is available. Thus, substantial equivalence is the starting point for safety evaluation not the end of it;
3. reporting on an Expert Consultation held in Geneva in 2000, they observed that the issue of the potential occurrence of unintended effects due to the genetic modification process is not unique for such foods but also occurs frequently in conventional breeding;
4. the Geneva meeting noted that, in general, very little is known about the potential long-term effects of any foods and that identification of such effects may be very difficult, if not impossible, due to the many confounding factors and the great genetic variability in food-related effects among the population. Thus, the identification of long-term consequences specifically attributable to genetically modified foods is highly unlikely. Epidemiological studies are not likely to identify such consequences ***given the high background of undesirable effects of conventional foods*** (our italics).

NOVEL FOOD REGULATION IN THE US

Prime responsibility for GM food safety falls to the Food and Drug Administration (FDA), but the Environmental Protection Agency (EPA) also has a role since some insect-resistant crop plants are themselves regarded as pesticides, part of the EPA's regulatory obligations. The US Department of Agriculture (USDA), with a more indirect role for food safety assessment, has a general responsibility for agricultural and environmental safety of commercial planting and field-testing genetically engineered plants. Its Animal and Plant Health Inspection Service (APHIS) regulates the movement, importation, field testing and deregulation of genetically engineered organisms through permitting and notification procedures (28). The USDA operates a Biosafety Library, a collection of biosafety/risk assessment documents and resources (29). A summary of the responsibilities of the US regulatory agencies can be found in reference 30.

The Food and Drug Administration

The FDA deals with the safety and labelling of all foods and animal feeds derived from crops. It has authority under the Federal Food, Drug, and Cosmetic Act (the Act) to ensure the safety and wholesomeness of most foods, except meat and poultry, including foods developed through modern biotechnology (i.e. embracing genetically modified foods). In 1990, the FDA issued the first regulation for the use of a recombinant DNA-produced food ingredient, fermentation-derived chymosin (rennet). In 1992, the agency published a policy statement to explain how foods and animal feeds derived from new plant varieties developed by both conventional and new breeding techniques are regulated under the Act. The 1992 policy provides "guidance to industry" that established a standard of care for assuring safety and wholesomeness (31). [A graphic view of the FDA's past and present role in food safety can be viewed as a Powerpoint slide presentation (32)].

Although the current UK-approved foods would have received US approval some years ago, it is likely that future products will also first come under scrutiny in the United States so more recent moves will be of interest to UK consumers. In 2001, the FDA published a ***Premarket Notice Concerning Bioengineered Foods***, proposing to require the submission to the agency of data and information regarding plant-derived bioengineered foods that would be consumed by humans or animals. The submission is to be made at least 120 days prior to the commercial distribution of such foods to ensure that the appropriate amount of information about bioengineered foods is available. This will help guarantee that all market entry decisions by the industry are made consistently and in full compliance with the law. The proposed action will permit the agency to assess on an ongoing basis whether plant-derived bioengineered foods comply with the standards of the Act (33). At around the same time, the agency announced new and extended guidelines (34).

The FDA publishes much explanatory material which can be found by trawling its website. One example is a paper dealing with the possibility of allergies caused by eating GM foods; it concludes “We are confident that the bioengineered foods that are currently approaching the market do not pose a safety concern for you or your family” (35).

The Environmental Protection Agency

This body is involved with the safety of foods (such as insect resistant maize as Bt-maize) classified as containing plant pesticides because of its role as the regulator of pesticides; the Bt bacterial protein, toxic to the European Corn Borer and other insects (important pests of this crop), is regarded as a pesticide even though it is expressed by the transgenic plant and not applied in the conventional manner as a spray.

In their document on biopesticides registration, the EPA observed that “the health effects assessment confirms the original findings that there are no unreasonable adverse health effects from these products. The human health assessment for the Bt plant incorporated protectants draws heavily on the science and toxicology of proteins. All the currently registered Bt plant-incorporated protectants are proteins. The source bacterium has been a registered microbial pesticide which has been approved for use on food crops. The Bt proteins approved for use in food are expected to behave as would be expected of a dietary protein. The Bt microbial pesticides have a long history of safe use without adverse health or environmental effects” (36); an accompanying report provides a detailed analysis of the scientific data (37).

General discussions of the regulatory process are available from Agriculture and Biotechnology Strategies (Canada) Inc. (38) and from the Council for Agricultural Science and Technology (39).

A comprehensive report by the U.S. National Biotechnology Policy Board (quoted in ref. 40), established by Congress and composed of representatives from the public and private sectors, concluded: “The risks associated with biotechnology are not unique, and tend to be associated with particular products and their applications, not with the production process or the technology ***per se***. In fact biotechnology processes tend to reduce risks because they are more precise and predictable. The health and environmental risks of not pursuing biotechnology-based solutions to the nation’s problems are likely to be greater than the risks of going forward.”

They go on: “These findings are consistent with the observations and recommendations of the United Kingdom’s House of Lords Select Committee on Science and Technology (41), which was very critical of that nation’s (i.e. the UK’s) policy of subjecting recombinant DNA biotechnology-derived products to additional regulatory requirements:

> ***As a matter of principle, GMO-derived products [i.e., those from genetically manipulated organisms, or recombinant organisms] should be regulated according to the same criteria as any other product. . . . U.K. regulation of the new biotechnology of genetic modification is excessively precautionary, obsolescent, and unscientific. The resulting bureaucracy, cost, and delay impose an unnecessary burden to academic researchers and industry alike.***”

Three joint FAO/WHO consultations, addressing specifically the question of the safety of rDNA biotechnology-derived foods, came to similar conclusions (40).

THE REGULATION OF NOVEL FOODS IN THE EUROPEAN UNION

The basic regulation governing novel foods in the EU is 258/97 which includes ***inter alia*** the statement “….. foods and food ingredients which contain genetically modified organisms and which are placed on the market must be safe for human health” (42)..

A questions and answers document reviews the current EU legislation, risk assessment and authorisation procedures, and considers the exact nature of the scientific advice underpinning GMOs in the EU, liability and the international context of GMOs in Europe (43).

An overview paper surveys a series of issues related to the approval and use of GM foods, including a summary of the current regulations, risk assessment procedures, changes due shortly, rules on the marketing of GM foods and lists of the scientific evidence supplied for various foods (44).

Various recent papers and proposals are directed to refining and extending the regulatory procedures:

- defining the responsibilities for food safety both by food and by feed businesses (45);
- one proposal provides for an improved, harmonised, uniform and transparent procedure for the safety assessment of genetically modified food, and a safety assessment and an authorisation procedure for genetically modified feed based on the same improved and transparent authorisation procedure as for genetically modified food; that authorisation should not be granted for a single use either as food or feed in cases where such products are likely to be used both as food and feed. It also provides for harmonised and comprehensive labelling requirements for genetically modified foods with the aim of providing the consumer with a real choice (46); and
- there is a further proposal for the authorisation and monitoring of genetically modified food and feed providing an improved, harmonised, uniform and transparent procedure for safety assessment of genetically modified food, and a safety assessment and an authorisation procedure for genetically modified feed, based on the same improved and transparent authorisation procedure as for genetically modified food (47).

A document detailing the EU regulatory framework for marketing GM crops in the EU (with links to products approved before May 1997 when Directive 90/220/EEC [on the deliberate release into the environment of genetically modified organisms, 23 April 1990] came into force (as well as later notifications under article 5 of the Novel Foods Regulation [EC] 258/97), is available on the Belgian Biosafety Server (48, 49). The status of crops approved for marketing was published by the Robert Koch Institut in 1999 (50).

A review of ongoing EC-funded research in GM food safety has recently been published (51). Other outcomes of EC-supported work are an interesting study, albeit largely directed to environmental effects, following the development of EU policy on GM crop safety regulation (52) and one in November 1999 dealing with the way the governing directive is working (53). A recent view of the principles governing EU regulatory thinking is provided by ***Communication from the Commission: Towards a Strategic Vision of Life Sciences and Biotechnology: Consultation Document*** (54).

THE REGULATION OF NOVEL FOODS IN THE UK

As a Member State of the European Union, the UK's regulatory procedures are in line with those agreed at EU level under Regulation 258/97. These are administered by the competent UK authority, the Food Standards Agency via its Advisory Committee on Novel Foods and Processes (ACNFP) (55). The home page of the Agency (56) can be followed through to the appropriate sections but, without help, it is not easy to unearth all the material relevant to the approval of GM foods. Before the Agency was founded in 2000, the competent authority was the Ministry of Agriculture, Fisheries and Food whose guidance notes on novel foods legislation remain accessible (57).

Relevant ACNFP documents include:

1. a list of the committee members (58);
2. the committee's view on the use of proper statistical data for evaluation purposes (59);
3. human studies (60);
4. toxicology (61);
5. general view on food safety (62);
6. fact sheet (63); and
7. safety of GM soybeans (64).

UK procedure for approval of novel foods and processes

To assist potential applicants identify the data required for their particular product, an interactive version of the decision tree has been developed which can be downloaded (65) or obtained by post from the ACNFP Secretariat. The decision tree establishes a set format for novel food applicants to follow.

Where a novel food is to be marketed first in the UK, an application is submitted to the UK Competent Authority. The request consists of a comprehensive summary report and a copy of all study reports necessary to support the data requirements identified in the guidelines that accompany the Regulation. The application should also include details of the proposed

labelling of the novel food. When an application contains all the relevant information, the UK will assess the information provided, this being carried out by the ACNFP who will in turn advise the UK Competent Authority, the Food Standards Agency. The ACNFP may, in the course of its assessment, seek the advice of other Committees with particular expertise such as the Food Advisory Committee, the Department of Health's Committee on Toxicity, or the Committee on Medical Aspects of Food Policy. Regulatory bodies can, and regularly do, withhold approval until they receive further information and are satisfied with the application.

As an illustration of the way the decision tree operates, the authors ran part of an application for a fictitious novel GM crop. We were informed that we needed to supply information to satisfy the following structured scheme:

1. Specification of the novel food
2. Effect of the production process applied to the novel food
3. History of the organism used as the source of the novel food
4. Effect of the genetic modification on the properties of the host organism
5. Genetic stability of the GMO
6. Specificity of expression on novel genetic material
7. Transfer of genetic material from GM microorganisms
8. Anticipated intake/extent of use of the novel food
9. Information from previous human exposure to the novel food or its source
10. Nutritional information on the novel food
11. Microbiological information on the novel food
12. Toxicological information on the novel food.

Proceeding through the tree giving arbitrary answers, we were asked under the section "Effect of the genetic modification on the properties of the host organism":

1. Has the host organism used for the GM a history of safe food use in the Community?
2. Are there any differences between the GM organism and the host solely the intended result of the GM?
3. Are there differences of nutritional, microbiological or toxicological significance, bearing in mind the way in which the novel food will be processed before consumption?

We were then informed of the outcome: "You will need to provide all relevant information on the host organism. (Later) schemes….discuss requirements for nutritional, microbiological and toxicological information."

The section "Information from previous human exposure to the novel food or its source" wanted responses to:

1. Is there information from previous direct, indirect, intended or unintended human exposure to the novel food or its source which is relevant to the Community situation with respect to production, preparation, population, lifestyles and intakes?
2. Is there information to demonstrate that exposure to the novel food is unlikely to give rise to nutritional, microbiological, toxicological and/or allergenicity problems?

Outcome: "You will need to provide all relevant information…."

Interested readers might wish to download their own copies of the decision tree and explore for themselves how it responds to different answers to the questions posed.

A list of applications to the ACNFP of foods for approval is available (66).

THE AUSTRALIAN NEW ZEALAND FOOD AUTHORITY

Although not directly germane to foods approved in the UK, it is of interest that the Australian and New Zealand authorities use criteria similar to those of the US, the EU and the UK as can be seen from their reports on Bt-maize varieties to which we refer in detail later in this report (67, 68). They have published their approach to GM food safety as a Powerpoint presentation (69).

THE SAFETY OF GM FEEDS

Since people eat meat and many animals are fed livestock feeds at certain times, the question of whether GM fodder may affect the animals directly or humans who eat those animals is clearly of interest. A survey of these questions is available on the University of Nebraska website (70).

AVAILABILITY OF INFORMATION

As for clinical drug approvals, the formal applications and supporting material as submitted to the regulatory authorities for the safety approval of transgenic food crops are not available to the public unless they have been made so by the applicants. The ***decisions*** of the regulatory bodies are, of course, published openly although, as with all technical information, an intending reader has to know where to look for them.

In practice, many of the companies have released extensive information into the public domain via websites, printed reports, papers reporting research findings in learned journals and technical publications in the usual way, and by other routes. We do not here propose to reference or comment in detail on this mass of data. Rather, for each of the approved foods, we will note in the next chapter and the appendices some of the most important material available and where it is to be found. Readers may then make their own evaluations of the data from those and other sources; as we will be dealing with the UK-***approved*** crops, it will also be appropriate refer to the published approval statements of the regulators which give the reasons for their decisions.

11. FOODS APPROVED FOR USE IN THE UK

The halesome parritch, chief of Scotia's food. — Robert Burns

This chapter describes in general terms the crops approved for human consumption. Details of the applications for use variously made to the regulatory authorities of Australia, Canada, the EU, Netherlands, New Zealand, Switzerland, the UK and the US, and/or their responses, are provided in Appendices A-H at the end of this Report.

At the present time, transgenic crops approved for human consumption in the UK and the EU are:

Maize ("corn" in the US):

1. event Bt-11 from Syngenta
2. event Bt-176 from Syngenta
3. event MON 810 (YieldGard Corn) from Monsanto.

The maize strains were modified genetically by insertion of a bacterial gene to produce the naturally occurring ***Bacillus thuringiensis*** (Bt) protein, Cry1Ab. This protects the plants from feeding damage by the European corn borer (***Ostrinia nubilalis***), the southwestern corn borer (***Diatraea grandiosella***) and the pink borer (***Sesamia cretica***). The Cry1Ab protein binds to specific receptors in the midgut of sensitive insects but does not affect mammals or insects lacking those receptors; it has selective toxicity for some specific lepidopteran insects but is harmless to humans, fish, wildlife and beneficial insects that can help control other pests. Bt proteins have been used safely for nearly 40 years in microbial insecticides for agricultural use, including organic farming.

EuropaBio have published a series of documents focusing on technical issues related to the safety of GM crops, including the assessment of substantial equivalence, provisions for detection and identification, requirements for molecular characterisation and protein safety evaluation, the appropriate use of animal feeding studies and the monitoring of GM crops. The documents summarise the current consensus of the member companies of EuropaBio's Plant Biotechnology Unit on the data necessary for notifications submitted under Council Regulation (EC) No 258/97 concerning novel foods and novel food ingredients; in the context of the present Report, the relevant crops in the series are maize (71) and soybeans (72).

Bt-11 also carries the ***pat*** gene from the bacterium ***Streptomyces viridochromogenes*** Tü494 which codes for the enzyme phopshinothricin acetyl transferase (PAT). This modifies and inactivates the herbicide glufosinate ammonium; its presence in the plant thus confers herbicide-tolerance. The gene was originally used as a selection marker to distinguish recombinant DNA cells from unmodified ones but the enzyme is expressed at a sufficiently high level to confer tolerance on the plant and allow this herbicide to be used in the field.

In Bt-176, the ***bar*** gene from ***Streptomyces hygroscopicus*** was also transferred to the corn as a selection marker. Like the ***pat*** gene in Bt-11, ***bar*** codes for the PAT protein but in insufficient quantities to confer herbicide tolerance.

Oilseed Rape ("canola" in North America):

1. MS1, RF1 (transformation events) PGS1 (variety code) from Aventis CropScience (formerly Plant Genetic Systems)
2. MS1, RF2 PGS2 from Aventis CropScience (formerly Plant Genetic Systems)
3. HCN92 variety code (also called Topas transformation event 19/2) from Aventis CropScience (formerly AgrEvo).

The MS1 and RF1 canola lines (***Brassica napus***) provide a pollination control system for production of hybrid oilseed rape (MS1 x RF1). The novel hybridisation system involves the use of two parental lines, a male sterile line MS1 and a fertility restorer line RF1. The transgenic MS1 plants do not produce viable pollen grains and cannot self-pollinate. In order completely to restore fertility in the hybrid progeny, line MS1 must be pollinated by a modified plant containing a fertility restorer gene, such as line RF1. The resultant F1 hybrid seed derived from cross between MS1 x RF1, produces hybrid plants that produce pollen and are completely fertile.

The transgenic line MS1 (B91-4) was produced by genetically engineering plants to be male sterile and tolerant to the herbicide glufosinate ammonium (as a selectable marker). The parental line MS1 contains the ***barnase*** gene for male sterility, isolated from ***Bacillus amyloliquefaciens***, a common soil bacterium and present in various organisms including bacteria and plants, and frequently used as a source for industrial enzymes. The barnase gene encodes for a ribonuclease enzyme (RNAse) expressed only in the tapetum cells of the pollen sac during anther development. The RNAse affects RNA production, disrupting normal cell functioning and arresting early anther development, thus leading to male sterility.

The transgenic lines RF1 (B93-101) and RF2 (B94-2) were produced by genetically engineering plants to restore fertility in the hybrid line and to be tolerant to the herbicide glufosinate ammonium (as a selectable marker). Transgenic RF1 plants contain the ***barstar*** gene (isolated from ***Bacillus amyloliquefaciens***) which codes for a ribonuclease inhibitor (barstar enzyme) expressed only in the tapetum cells of the pollen sac during anther development. The ribonuclease inhibitor (barstar enzyme) specifically inhibits barnase RNAse expressed by the MS1 line. Together, the RNAse and the ribonuclease inhibitor form a very stable one-to-one complex in which the RNAse is inactivated. As a result, when pollen from the restorer lines RF1 or RF2 are crossed to the male sterile line MS1, the resultant progeny express the RNAse inhibitor in the tapetum cells of the anthers allowing hybrid plants to develop normal anthers and restore fertility.

These canola lines contain the ***bar*** gene conferring tolerance to the post-emergence, broad-spectrum phosphinothricin herbicides (glufosinate). The ***bar*** gene, isolated from the common soil microorganism ***Streptomyces hygroscopicus***, encodes a phosphinothricin acetyl transferase (PAT) enzyme. The active ingredient in phosphinothricin herbicides is glufosinate ammonium which acts by inhibiting the plant enzyme glutamine synthetase, leading to the accumulation of phytotoxic levels of ammonia killing the plant within hours of application. PAT detoxifies glufosinate ammonium by acetylation into an inactive compound, eliminating its herbicidal activity. The herbicide tolerance trait was introduced into the canola lines as a selectable marker to identify transformed plants cells in the laboratory, and as a field selection method to obtain a near 100% hybrid seed.

Canola (***Brassica napus***) line HCN92 (synonyms: Topas19/2, Innovator) was similarly

developed through a specific genetic modification to allow the use of glufosinate ammonium, the active ingredient in phosphinothricin herbicides such as Liberty®. The ***pat*** gene, which encodes the PAT enzyme and confers tolerance to glufosinate ammonium, was isolated from the common aerobic soil actinomycete, ***Streptomyces viridochromogenes*** strain Tü 494 and introduced into the parent canola line.

It is important to bear in mind that the human food product produced from oilseed rape is a highly refined oil. The genetic modification of the novel rapeseed strains involves the introduction of DNA (carrying the transferred genes) and the protein product(s) for which they code, Since neither DNA nor proteins are soluble in oil and refined edible oils therefore contain neither of them (73-78), such oils are regarded as substantially equivalent to similar oils from non-transgenic plants. With increasing sensitivity of detection methods, it may be the case that traces of DNA will sooner or later be found in refined oils but those methods are now so exquisite that any such traces will be virtually at the level of single molecules. While consumers wanting to avoid transgenic foods on principle will wish to know whether a particular oil originates from such a source, any health implications (and none have been found with any of these gene constructs) would be in any event be literally infinitesimal.

Soybeans:

Roundup Ready® Soybean Event GTS 40-3-2 (GTS presumably stands for “Glyphosate tolerant soybean”) from Monsanto.

Roundup Ready® soybean varieties confer tolerance to glyphosate (the active ingredient of a widely-used herbicide) by production of the CP4 enolpyruvylshikimate-3-phosphate synthase (EPSPS) protein. One of the class of EPSPS proteins ubiquitous in plants and microorganisms, enolpyruvylshikimate-3-phosphate synthase catalyses a step in the shikimic acid pathway for the biosynthesis of aromatic amino acids. Inhibition of the enzyme by glyphosate leads to a deficiency in the production of aromatic amino acids and lack of growth in plants. This biosynthetic pathway is absent from mammals, birds and aquatic life forms, leading to the selective activity of glyphosate in plants and its low mammalian toxicity. Event 40-3-2 was produced by introduction of the naturally glyphosate-tolerant ***cp4*** EPSPS coding sequence derived from a common soil bacterium into the soybean genome.

Tomatoes:

B, Da, F from Zeneca Seeds

The tomato lines B, Da and F were developed using recombinant DNA techniques (“genetic engineering”) to display the trait of delayed ripening of tomato fruit. These transgenic tomato lines contain a partial polygalacturonase (PG) gene that encodes for the PG protein, a pectin-degrading enzyme derived from tomato. The lines differ slightly in that Da and F contain the partial PG gene in the sense orientation while line B contains a partial antisense PG gene, essentially a reverse copy. The presence of the partial PG gene, in either sense or antisense orientation, suppresses the expression of endogenous PG enzyme at the onset of fruit ripening. While Zeneca filed for registration of three lines in the US and Canada, in the UK and Europe registration of the F line only was sought.

Note the use of the word “event”: this describes the initial genetic manipulation in a strain which, through conventional cross-breeding, becomes the parent of many varieties bred

specifically for cultivation under local different climatic or soil conditions. The original event may be bred into hundreds or even thousands of different varieties.

GENERAL ARTICLES

As well as the specific documentation detailed in the appendices, there are number of publications reviewing the biosafety of GM products generally or specifically. A few are listed here and their sources given together with the other references:

6. American Medical Association food biotechnology media briefing (79).
7. Donaldson and May: ***Health implications of genetically modified foods*** (80).
8. ***Development of new methods for safety evaluation of transgenic food cr***ops (81).
9. Mycotoxins in maize (82, 83)
10. Report of the OECD workshop on the toxicological and nutritional testing of novel foods (84).
11. Joint FAO/WHO expert consultation on allergenicity of foods derived from biotechnology (85).
12. Joint FAO/WHO expert consultation on foods derived from biotechnology (86).
13. Pesticides present in plants (87).

12. EVALUATING THE DATA

Every one is bound to bear patiently the results of his own example. — Phaedrus

Having reviewed the evidence and how it can be accessed, we cannot but conclude that the people concerned with developing, promoting and approving transgenic foods for public consumption have been thorough. That is not to say that they may always have been encompassed every eventuality and possibility because anything anyone does must inevitably have an element of uncertainty about it; we need hardly stress again that one cannot know the future. But inasmuch as one can use current information and past experience to decide whether or not to go ahead, the responsible authorities have been properly diligent and accountable. They have agreed a reasonable set of rules and criteria, and have applied them in a trustworthy manner.

It may be the case (and with good reason, some would say) that in certain countries public confidence in government and its agencies has taken a knock or two in recent years. Nevertheless, details of the regulatory processes for the approval of transgenic foods are very similar for the different countries and sufficiently open for individuals to make up their own minds from publicly available sources. We hope that our efforts will enable interested readers to do just that and will counter assertions that the regulatory procedure is secret, arbitrary and inadequate.

CLINICAL DRUGS AND NOVEL FOOD TESTING PROCEDURES COMPARED

We noted near the beginning of this Report that some critics of agricultural biotechnology products advocate full pharmaceutical testing of the GM-derived foods; we have accordingly included an outline of drug testing regulations to allow a comparison to be drawn. Much of the GM food testing requirement actually does parallel drug evaluation and we have commented on why, in our opinion, it would be impossibly difficult to put novel foods through the whole elaborate sequence of the clinical test procedures. Nor do we think it necessary.

There are, in our view, two primary considerations in making such a comparison: relevance and cost. Clinical drugs are designed to influence specific effects in the extremely complex organisation of the human condition. They are evaluated in laboratory animals (and later in human patients) in acute, subacute and sometimes chronic studies. Large increments of the human dose are possible because the pharmaceutical is usually a single defined chemical substance and not bulky. Such drugs must clearly be effective or they are not worth having. But they must not have undesirable side effects which take away with one hand what might be given by the other. The discovery of new and effective drugs usually carries with it a strong element of chance: the purpose-design of clinical drugs based upon a detailed understanding of human biochemistry remains in its infancy.

Nevertheless, it is possible to make progress although with great difficulty — and expense. The chart from AstraZeneca reproduced in Chapter 7 shows the enormous attrition rate of prospective new drugs: up to 10,000 potential products in the laboratory may reduce to only one new drug being launched, at a cost approaching $500 million. The likely return on an investment of that magnitude in the context of so much uncertainty must clearly be sufficient

to encourage taking the risks or we would never have any new drugs.

The GM food position is very different. To start with, an approved product crop is overwhelmingly familiar: a plant already containing about 30,000 genes has one or two more genes added or a couple altered. It makes a difference, of course — that is why it is done — but it has a limited effect both on the plant and on any foods produced from it. Nevertheless, those possibly minor differences are important; they are the reason for mounting a careful investigation of the new construct to ensure that neither the products of the added genes, nor any consequences for the plant metabolism as a whole, render food products unsafe for consumption.

Secondly, new genes and their products introduced into a plant are well recognised and characterised; because they are known, they can be examined and tested quite specifically. Currently approved GM foods contain a single new defined substance, the gene product, which is normally a digestible protein and which can be tested in typical toxicological studies appropriate for a rapidly digested protein. In addition, there are tests for potential allergenicity. If the gene product is not readily digestible or otherwise more complex the necessary additional toxicity testing is undertaken, fully analogous to the procedures applied to pharmaceuticals.

Furthermore, the novel GM food is tested for compositional content according to published OECD standards as well as for possible nutritional impacts (energy value, the presence of anti-nutrients, etc.) on health. Typically this makes use both of compositional data and animal feeding studies.

If, having followed-up any difference from the conventional crop, the new food appears to be comparable, it may be judged to be as safe and nutritious as its antecedent. This process of looking at the new component as well as the whole new crop is every bit as rigorous in its toxicological and safety aspects as those for a pharmaceutical.

Nobody will claim that every possible effect can be characterised in advance: that is an aspect of no product of any sort ever being 100% safe or of knowing what tomorrow may bring. As we have described in some detail, the regulatory authorities meet that position by demanding extensive and detailed examination of all new GM products to an extent wholly unknown in any other aspect of food technology. Furthermore, plans are in train to mount post-marketing monitoring in order to pick up any untoward effects in use should they occur. Post-launch monitoring does already exist with clinical drugs and very occasionally a drug is withdrawn or its use contraindicated in particular circumstances.

And thirdly, of course, the transgenic technology has economic overtones very different from those of clinical drugs: the choice of eating or not eating, planting or not planting is not the acute one of using or not using a drug to treat an illness. Moreover, the markets for the two categories of product have few points of similarity: one is sold by the milligramme (perhaps on prescription and on the specific recommendation of a medical adviser), the other bought by the pound or even by the sack as the personal decision of the consumer.

HAZARDS AND RISKS

We come back to the question of the nature and likelihood of a hazard occurring, and hence

of a reasonable risk. Should we refrain from every activity which might conceivably carry a risk of hazard? Should we outlaw every food which has been shown in some circumstance to be harmful? Should we anyway test every food against every possibility? Should we ban tractors from agriculture? Some people can make a good case for doing so: they are noisy and smelly, intrude on the peace of the countryside, use fossil fuel and emit gases which might contribute to a deterioration of our climate, compact the ground over which they travel and inevitably impact the local wildlife. Should we go back to horses (or people) to pull ploughs? Indeed, should we use agricultural implements of any sort?

In our view, it is essential to retain a sense of proportion. Inasmuch as GM crops and foods have value, we favour their being available for those who want them and are prepared to assume the minuscule risk in their use, a risk less than for any other comparable foodstuffs. In time, we may all become so used to them that none of us any longer goes in fear and trembling, demanding testing, testing, testing without limit. But we are not there yet. This remains a fairly new technology; although products have been on the market for several years without any reported ill effects, the populace at large, even in the countries of North America where there is general acceptance, are not sufficiently comfortable with transgenic foods and crops to reduce the stringency of the regulatory procedures. Regulation at the present time is about right for present circumstances, rigorous enough to spot health hazards while allowing a reasonable level of development and not so stringent as totally to abolish investment in taking the technology forward for the greater benefit of mankind.

THE CRITICS

Any activity, novel or commonplace, may not turn out the way one might hope and expect. It was (and is) as reasonable for people to point this out with respect to transgenic crops and foods as for anything else. What is not reasonable is to pile one upon another all the conceivable failings that imagination can accumulate and then to hold up one's hands in horror and announce something close to the end of life as we know it. Things will go wrong — but we cannot live our lives assuming that everything will go wrong at the same time. To take a medical example, somebody who has contracted cancer (quite bad enough in itself) is unlikely simultaneously to have acquired cardiovascular disease, diabetes, multiple sclerosis and ingrowing toe nails. We live our lives with that understanding; experience has widely shown that, as we become used to dealing with new ideas and new methods, we are able to anticipate, detect and put right most technological failings, hopefully with minor consequences.

It might be ***possible*** to make a GM food which is toxic, allergenic and generally poisonous, just as it would be ***possible*** to put deadly nightshade into a salad. But there would no point in a commercial company (even a hated "multinational") doing either as a way of winning hearts and minds on the way to long-term acceptability and profit. The livelihoods of companies large and small depend on their taking good care of their clients and customers for fear of losing them to competitors, while it is the job of governments to ensure that competition is indeed fostered.

THE PRECAUTIONARY PRINCIPLE

Those same critics of agricultural biotechnology (and of much else besides) often take refuge in the ***precautionary principle***, an elaborate reiteration of the simple admonition "look before

you leap". The concept is discussed in detail by Morris and others (88).

The precautionary principle plays an important part in European Union thinking about the regulation of transgenic foods and crops; Commissioner David Byrne outlined the Commission position in a major speech (89) while an important EU position paper explores many of the implications (90). Curiously, while the precautionary principle is variously described in the EU paper, it is not defined. The paper notes that although the principle is not explicitly mentioned (in the Treaty) except in the environmental field, its scope is far wider and covers those specific circumstances where scientific evidence is insufficient, inconclusive or uncertain, and there are indications through preliminary objective scientific evaluation that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the chosen level of protection — if you see what they mean.

The EU paper goes on to point out that the precautionary principle has been developed primarily in the context of environmental policy and quotes the Ministerial Declaration of the Second International Conference on the Protection of the North Sea (1987) which states that

> ***"in order to protect the North Sea from possibly damaging effects of the most dangerous substances, a precautionary approach is necessary which may require action to control inputs of such substances even before a causal link has been established by absolutely clear scientific evidence". Article 3 (Principles) of the Convention of Climate Change (1992) continues: "The Parties should take precautionary measures to anticipate, prevent or minimise the causes of climate change and mitigate its adverse effects. Where there are threats of serious or irreversible damage, lack of full scientific certainty should not be used as a reason for postponing such measures, taking into account that policies and measures to deal with climate change should be cost-effective so as to ensure global benefits at the lowest possible cost. To achieve this, such policies and measures should take into account different socio-economic contexts, be comprehensive, cover all relevant sources, sinks and reservoirs of greenhouse gases and adaptation, and comprise all economic sectors."***
>
> ***"At Community level the only explicit reference to the precautionary principle is to be found in the environment title of the EC Treaty, and more specifically Article 174. However, one cannot conclude from this that the principle applies only to the environment (Annex I, Refs. 2 and 3). Although the principle is adumbrated in the Treaty, it is not defined there."***
>
> ***"Like other general notions contained in the legislation, such as subsidiarity or proportionality, it is for the decision-makers and ultimately the courts to flesh out the principle. In other words, the scope of the precautionary principle also depends on trends in case law, which to some degree are influenced by prevailing social and political values."***
>
> ***"However, it would be wrong to conclude that the absence of a definition has to lead to legal uncertainty. The Community authorities' practical experience with the precautionary principle and its judicial review make it possible to get an ever-better handle on the precautionary principle."***

The precautionary principle is obviously a sensible idea but those who quote it to excess

habitually ignore its symmetry. The choice is not between an action and nothing. It is between taking an action ***and not taking that action***; both have consequences which need thinking about. Standing on a tropical beach, wondering whether to paddle a leaky canoe across the possibly shark-infested lagoon to an offshore island a mile or so away, the precautionary principle would advise caution and suggest that perhaps you should keep your feet on the ground. Turn the question round the other way, bear in mind that the lava from a nearby volcanic eruption is beginning to encroach upon the beach, and ask: “is this a good place to stay?” That very same precautionary principle might counsel getting out without delay and, if paddling the canoe across the lagoon is the only way, so be it.

That view of the precautionary principle sounds very much like the attitude of the U.S. National Biotechnology Policy Board when they commented (as we observed several chapters ago) that “the health and environmental risks of not pursuing biotechnology-based solutions to the nation’s problems are likely to be greater than the risks of going forward” (40).

HOW TO DECIDE?

It is all too easy to work oneself up into a cold sweat worrying about everything that can go wrong with anything at all, let alone eating GM food; according to some authorities, dining off butter and cheese and good red meat can all be very risky things to do. So cold is the sweat that it becomes all too easy to forget about the alternatives. A pragmatic response after as full a review of the evidence as possible seems to us to be the best way of making a decision. Applying the precautionary principle as well as other styles of judgement should mean prudence but not paralysis: take a sensible and rational view of going forward without being scared of your own shadow.

13. CONCLUSIONS

Wearing all that weight
Of learning lightly like a flower.
— Alfred Lord Tennyson

As biochemists, our reading of the publicly-available information on transgenic food safety has offered us not one indication of a hazard to human health from any of the GM crop foods so far approved for use in the UK. This view is clearly supported by the decisions of competent regulatory bodies in the US, the UK, the EU, Canada, Australia, New Zealand and elsewhere, authorities who are not only more skilled and experienced in such matters than we are but who have also had access to additional private information. The absence of a single report — from anywhere in the world where such products have been consumed — of any human health effect cannot be ignored; it adds significant further weight to these conclusions.

So: one-hundred percent safe? With foods approved for UK use, for all practical purposes the answer is clearly “yes” but we have pointed out many times that nobody can know the future and 100% certainty is not possible for anything. An absence of harm to human health so far does not ***guarantee*** that nothing will turn up tomorrow or next week. Since that is equally true for all foods, those from GM sources must be at least as safe as or safer than all the others because novel foods, including transgenics, have undergone extensive testing and many possible health hazards have already been eliminated; that is not true for any other food category.

We might take a last look at kiwifruit. In more than 30 years, no reported health problems have appeared in the UK except for some allergenic responses. But in 60 years…..who knows? Come back in 2031.

14. APPENDIX A

TRANSGENIC MAIZE EVENT Bt-11 (SYNGENTA)

For a general description of this genetic construct see BT11 (X4334CBR, X4734CBR) on the University of Nebraska website (91).

Information on the product as part of the formal application for approval made to the Swiss authorities in 1998 was published May, 2001 (partly in German and partly in English — the section on biosafety is in English) under the title ***Unterlagen zur Zulassung und Bewilligung des gentechnisch veränderten Mais (Bt 11 ex Sandoz)*** ("Evidence for a permit for the genetically-modified maize [Bt 11 ex Sandoz]") (92). Note that the published application records that some of the appendices have not been included. On October 14th, 1998, the Swiss Health and Agricultural Authorities approved the product for food and animal feed use.

Health Canada's "review of the information presented in support of the food use of insect resistant and herbicide tolerant BT11 corn concluded that this corn does not raise concerns related to human food safety. Health Canada is of the opinion that products from Bt11 corn are as safe and nutritious as those available from current commercial corn varieties. Health Canada's opinion pertains only to the food use of this….corn. Issues related to growing….in Canada and its use as animal feed are addressed separately….." (93). A separate document reports that "Unconfined release into the environment, including feed use, of the corn hybrids X4334CBR, X4734CBR, and other Z. mays lines derived from them, but without introduction of any other novel trait, is therefore authorized" (94).

A Draft Final Risk Analysis Report from the Australia New Zealand Food Authority (ANZFA) (95) addresses many of the safety aspects of Bt-11. Note, however, that the report is not dated we have not been able to locate a definitive final version of this document. The safety assessment was performed according to the ANZFA safety assessment guidelines and considered:

1. the nature of the genetic modification;
2. general safety issues such as novel protein expression and the potential for transfer of novel genetic material to cells in the human digestive tract;
3. toxicological issues; and
4. nutritional issues.

It was concluded that:

1. the introduced genes in insect-protected, herbicide-tolerant Bt-11 corn are not considered to produce any increased public health and safety risk;
2. on the basis of the data provided in the application, food derived from insect-protected, herbicide-tolerant Bt-11 corn is equivalent to food derived from any other commercial varieties of corn in terms of its safety and nutritional adequacy; and
3. that the food was as safe for human consumption as food from other commercial corn varieties.

In February 2001, referring to ***Application A386 – Food derived from insect-protected, herbicide-tolerant Bt-11 corn***, "The Board approved the Inquiry Report for the approval of food from insect-protected corn which has been genetically modified for protection from

attack by lepidopteran pests, particularly the European corn borer and is tolerant to applications from the herbicide glufosinate-ammonium. The proposed draft variations to the ***Food Standards Code*** will now be recommended to Ministers for adoption" (96).

Considering an application from Northrup King, the FDA resolved "that corn lines containing transformation event Bt 11 are not materially different in composition, nutrition and safety from corn currently grown, marketed and consumed for animal feed or human food. At this time, based on Nortrhrup King's description of its data and analyses, the Agency considers Northrup King's consultation….to be complete (97).

The Office of Pesticide Programs of the US Environmental Protection Agency reported in April 2000 that:

- no mammalian toxicity is anticipated from dietary exposure to the genetic material necessary for the production of the subject active and inert plant pesticidal ingredients;
- the potential for Cry1Ab protein to be a food allergen is minimal; and
- the establishment of tolerances is not necessary to protect the public health and therefore exemptions from tolerances apply to ***Bacillus thuringiensis*** Cry1Ab delta-endotoxin and the genetic material necessary for its production in all plants (98).

The European Union approval decision reads in part as follows:

"Article 1

1. Without prejudice to other Community legislation, in particular Regulation (EC) No 258/97 of the European Parliament and the Council (4), and subject to paragraphs 2 and 3 of this Article, consent shall be given by the competent authorities of the United Kingdom to the placing on the market of the following product, notified by Novartis Seeds Inc. (Ref. C/GB/96/M4/1):
   grains of genetically modified maize line Bt-11 containing:
   (a) a synthetic version of the cryIA (b) gene derived from ***Bacillus thuringiensis*** subsp. Kurstaki strain HD1 under the control of a 35S promoter from Cauliflower Mosaic Virus, and IVS 6 intron from the maize alcohol dehydrogenase gene and the nopaline synthase terminator sequence of ***Agrobacterium tumefaciens***, and
   b) a synthetic version of the pat gene derived from ***Streptomyces viridochromogenes*** under the control of a 35S promoter from Cauliflower Mosaic Virus, an IVS 2 intron from the maize alcohol dehydrogenase gene and the nopaline synthase terminator sequence of ***Agrobacterium tumefaciens***
2. The consent shall cover grains from progenies derived from crosses of maize line Bt-11 with any traditionally bred maize imported into the Community. The consent shall cover the placing on the market of the product to be used as any other maize grain but not for cultivation." (99).

In the Dutch assessment report of June 2000, the Committee was of the opinion that the consumption of Bt11 sweet maize and the foods and food ingredients produced from it are just as safe for human consumption as maize and maize products that have not been genetically modified (100).

15. APPENDIX B

TRANSGENIC MAIZE EVENT Bt-176 (SYNGENTA)

For a general description of this construct see 176 on the University of Nebraska website (101).

The general pattern of information is similar to that of Bt-176. The Swiss approval application made in 1998 is published (again partly in German and partly in English — the section of biosafety is once more in English) under the title ***Unterlagen zur Zulassung und Bewilligung des gentechnisch veränderten Mais (Bt 176 Mais ex Ciba).***(102). Note that the published application records that some of the appendices have not been included. In January 1998, the Swiss authorities approved Bt-176 for both food and animal feed uses.

A Final Risk Analysis Report from the Australia New Zealand Food Authority (ANZFA) (103) is organised like the one for Bt-11. The safety assessment followed similar lines and the conclusions were identical. It is concluded that:

1. the introduced genes in food derived from insect-protected Bt-176 corn are not considered to produce any increased public health and safety risk;
2. on the basis of the data provided in the application, food derived from insect-protected Bt-176 corn is equivalent to food derived from other commercial varieties of corn in terms of its safety and nutritional adequacy.

Based on the data submitted in the application, ANZFA concludes that food derived from insect-protected Bt-176 corn is as safe for human consumption as food from other commercial corn varieties, and therefore recommends that the Australian Food Standards Code (Volume 1) and the recently adopted joint Australia New Zealand Food Standards Code (Volume 2) be amended to give approval to the sale of such food in Australia and New Zealand. The proposed amendment to Standard A18 and Standard 1.5.2 is provided in Attachment 1.

In February 2001, referring to ***Application A385 – Food derived from insect-protected Bt-176 corn***, “The Board approved the Inquiry Report for the approval of food from insect-protected corn which has been genetically modified for protection from attack by lepidopteran pests, particularly the European corn borer. The proposed draft variations to the ***Food Standards Code*** will now be recommended to Ministers for adoption” (104).

In their ***Note to File of July 14th, 1995***, the FDA said: “Ciba-Geigy has concluded that no issues of concern regarding the food or feed safety were raised by their analysis of their Event 176 corn. At this time, based on Ciba-Geigy’s description of its data and analyses, the Agency considers Ciba-Geigy’s consultation on corn grain (kernels) from their Event 176 corn line to be complete” (105).

Health Canada’s review of Bt-176 reached conclusions identical to those for Bt-11: “.....the information presented in support of the food use of insect resistant and herbicide tolerant BT11 corn concluded that this corn does not raise concerns related to human food safety. Health Canada is of the opinion that products from Bt11 corn are as safe and nutritious as those available from current commercial corn varieties. Health Canada’s opinion pertains only

to the food use of this….corn. Issues related to growing….in Canada and its use as animal feed are addressed separately….." (106). The Canadian Food Inspection Agency reported: "Based on the review of submitted data and information, the Feed Section of the Plant Products Division has concluded that the novel traits do not in themselves raise any concerns regarding the safety or nutritional composition of Event 176. Grain corn and its various fractions, and corn oil are currently listed in Schedule IV of the ***Feeds Regulations*** and are, therefore, approved for use in livestock feeds in Canada. As Event 176 has been assessed and found to be substantially equivalent to traditional corn, Event 176 and its by-products are considered to meet present ingredient definitions and are approved for use as livestock feed ingredients in Canada." (107).

European Union approval was given on January 23rd, 1997 as follows:

"Article 1

1. Without prejudice to other Community legislation and subject to paragraphs 2 and 3, the French authorities shall give consent to the placing on the market of the following product, notified by Ciba-Geigy Limited (Ref. C/F/94/11-03), in accordance with Article 13 of Directive 90/220/EEC.
   The product consists of inbred lines and hybrids derived from a maize (***Zea mays*** L.) line (CG 00256-176) which has been transformed using plasmids containing:
   (i) phosphinothricin acetyltransferase), under the regulation of the 35S promoter and the 35S terminator from the cauliflower mosaic virus (CaMV);
   (ii) two copies of a synthetic truncated gene encoding an insect control protein representing the active portion of the CryIA(b) delta-endotoxin, from ***Bacillus thuringiensis*** subsp. Kurstaki strain HD1-9 and containing intron 9 from the maize phosphoenolpyruvate carboxylase gene; the first copy is under the regulation of a promoter from the maize phosphoenolpyruvate carboxylase gene and the CaMV 35S terminator, and the second copy is regulated by a promoter derived from a maize calcium-dependent protein kinase gene and the CaMV 35S terminator;
   (iii) the prokaryotic gene ***bla*** (coding for a beta-lactamase conferring resistance to ampicillin) under prokaryotic promoter.
2. The consent covers any progeny derived from crosses of this product with any traditionally bred maize.
3. Without prejudice to other labelling required by Community legislation, the label of each package of seeds shall indicate that the product:
   – protects itself against corn borers, and
   – has increased tolerance to the herbicide glufosinate-ammonium (108).

A subsequent decision (***Opinion on the invocation by Germany of Article 16 of Council 90/220/EEC regarding the genetically modified BT-MAIZE LINE CG 00256-176 notified by CIBA-GEIGY [now NOVARTIS], notification C/F/94/11-03 [SCP/GMO/276Final – 9 November 2000] [Opinion adopted by written procedure following the SCP meeting of 22 September 2000]***) noted that "Although the frequency of horizontal gene transfer between the GM-maize and the ruminal or intestinal bacteria may have been underestimated, the significance of such an event in this particular case would be negligible given regard to the high background presence of the ***bla*** gene in the environment. Consequently there is no need to reconsider the previous Committee opinion on CG-00256-176 in this respect." (109).

In their study "Bt corn in the diet of broiler chickens", Brake & Vlachos (110) found that

broilers raised on diets prepared from the transgenic corn exhibited significantly better feed conversion ratios and improved yield of the ***Pectoralis minor*** breast muscle. Although it was not clear whether this enhanced performance was attributable to the transgenic corn ***per se***, or due to possible slight differences in overall composition of the formulated diets, the transgenic corn in this study clearly had no deleterious effects on the animals.

The Office of Pesticide Programs of the US Environmental Protection Agency reported in April 2000 that the genetic material necessary for the production of the ***Bacillus thuringiensis*** Cry1Ab delta-endotoxin are the nucleic acids (DNA) which comprise (1) genetic material encoding the Cry1Ab delta-endotoxin and (2) its regulatory regions. “Regulatory regions” are the genetic material that control the expression of the genetic material encoding the Cry1Ab delta-endotoxin, such as promoters, terminators, and enhancers. DNA is common to all forms of plant and animal life and the Agency knows of no instance where these nucleic acids have been associated with toxic effects related to their consumption. These ubiquitous nucleic acids as they appear in the subject active ingredient have been adequately characterised by the applicant. Therefore no mammalian toxicity is anticipated from dietary exposure to the genetic material necessary for the production of the ***Bacillus thuringiensis*** Cry1Ab delta-endotoxin in corn (111).

16. APPENDIX C

TRANSGENIC MAIZE EVENT MON810 (MONSANTO)

General descriptions of the product can be downloaded from the University of Nebraska website (112) and from Monsanto (113). Monsanto's own safety assessment document is "Safety Assessment of YieldGard Insect-Protected Corn Event MON 810" (114).

Health Canada approved the product in June 1997 (115).

The European Union reported on February 10th, 1998:

The Commission requested the Scientific Committee on Plants to consider whether the production, import and processing of an insect-protected maize line MON810 (expressing the ***Btk*** endotoxin) and progeny derived thereof is likely to cause any adverse effects on human health or the environment. The Committee was also asked to assess the risk management strategies to be used to minimise the likelihood of resistance developing in the target pests. In the assessment of the dossier provided against the criteria set out in Directive 90/220/EC, the Committee has reached the following conclusions:

1. The Committee after examining and considering the existing information and data provided in the dossier, against the background of available knowledge in the areas concerned, considers that there is no evidence to indicate that the seeds of insect-resistant maize (expressing the cry1A(b) gene and protein) when grown, imported and processed in the manner indicated, are likely to cause adverse effects on human or animal health and the environment.
2. The Committee was also of the opinion that the proposed plan for risk assessment with regard to Btk endotoxin resistance development provides an adequate framework to delay the onset of such resistance in the target pest. The Scientific Committee should be kept informed of monitored progress in the field." (116).

A second report of April 22nd, 1998 stated:
"Article 1

1. Without prejudice to other Community legislation, in particular Council Directives 66/402/EEC (4) and 70/457/EEC (5) and Regulation (EC) No 258/97 of the European Parliament and the Council (6), and subject to paragraph 2 of this Article, consent shall be given by the competent authorities of France to the placing on the market of the following product, notified by Monsanto Europe SA (Ref. C/F/95/12-02):
2. inbred lines and hybrids derived from maize line MON 810 containing the ***cryIA (b)*** gene from ***Bacillus thuringiensis*** subsp. Kurstaki under the control of the enhanced 35S promoter from cauliflower mosaic virus and an intron from the gene coding for the heat shock protein 70 from maize.

   The consent shall cover any progeny derived from crosses of the product with any traditionally bred maize." (117).

17. APPENDIX D

TRANSGENIC OILSEED RAPE MS1, RF1 ⇒ PGS1 (Aventis CropScience)

For a general description of this genetic construct see MS1, RF1 PGS1 on the University of Nebraska website (118).

The Australian New Zealand Food Authority concluded that on the basis of the data submitted with the application and evidence obtained from the scientific literature:

1. the introduced genes in canola lines Topas 19/2, T45, Ms1, Ms8, Rf1, Rf2 and Rf3 are not considered to produce any additional public health and safety risk;
2. oil derived from the genetically modified canola lines is equivalent to other commercial non-genetically modified canola varieties in terms of its food safety and nutritional adequacy.

In a recommendation based on the data submitted in the application, ANZFA concludes that food oil derived from canola lines Topas 19/2, T45, Ms1, Ms8, Rf1, Rf2 and Rf3 and subsequent crosses is as safe for human consumption as food from other commercial canola varieties, and therefore recommends that the Australian Food Standards Code (Volume 1) and the recently adopted joint Australia New Zealand Food Standards Code (Volume 2) be amended to give approval to the sale of such food in Australia and New Zealand. The proposed amendment to Standard A18 and Standard 1.5.2 is provided in Attachment 1 (119).

The EU report (120) adopted the following decision:
“Article 1

1. Subject to the provisions laid down in Council Directive 69/208/EEC (5) and to the conditions outlined in paragraph 2, the authorities of the United Kingdom shall consent to the placing on the market of the following product, notified by Plant Genetic Systems (Reference C/UK/94/M1/1), under Article 13 of Directive 90/220/EEC.

   The product comprises of living seeds of a hybrid swede-rape (***Brassica napus*** L. oleifera Metzq.) derived using:

   (a) the progeny of the male sterile swede-rape line MS1Bn (B91-4) cultivar Drakkar containing the ***barnase*** gene from bacillus amyloliquefaciens coding for ribonuclease, the ***bar*** gene from ***Streptomyces hygroscopicus*** coding for phosphinothricin acetyl transferase, the ***neo*** gene from ***Escherichia coli*** coding for neomycin phosphotransferase II, the promoter ***PSsuAra*** from ***Arabidopsis thaliana***, the promoter ***PNos*** from ***Agrobacterium tumefaciens***, the promoter ***PTA29*** from ***Nicotiana tabacum***; and

   (b) the progeny of the fertility restoration swede-rape line RF1BN (B93-101) cultivar Drakkar containing the ***barstar*** gene from ***Bacillus amyloliquefaciens*** coding for ribonuclease inhibitor, the ***bar*** gene from ***Streptomyces hygroscopicus*** coding for phosphinothricin acetyl transferase, the ***neo*** gene from ***Escherichia coli*** coding for neomycin phosphotransferase II, the promoter ***PSsuAra*** from ***Arabidopsis thaliana***, the promoter ***PNos*** from ***Agrobacterium tumefaciens***, the promoter ***PTA29*** from ***Nicotiana tabacum***.

2. The conditions of the consent are as follows:

   (a) The consent covers the seeds of all hybrids between non-genetically modified swede-rape and the genetically modified swede-rape described in paragraph 1 but does not cover the seeds of any hybrids resulting from a combination of any genetically modified plants other than those described in paragraph 1.

   (b) The consent only covers the notified use of the product for growing for obtaining seed, but does not extend to the use for human food or animal feed, without prejudice to any future assessment of the product for such use.

   (c) In addition to any other labelling, it will be indicated on the label of each package of seeds that the product is tolerant to the herbicide glufosinate ammonium; and that the product is to be used only for obtaining seed and not for human food or animal feed.

18. APPENDIX E

TRANSGENIC OILSEED RAPE MS1, RF2 ⇒ PGS2 (Aventis CropScience)

For a general description of this genetic construct see MS1, RF2 =>PGS2 on the University of Nebraska website (121).

The ANZFA conclusions referred to above (119) include this strain.

Health Canada reported (122):

“Since only the processed oil from transgenic MS1, RF2, or lines derived therefrom, will be available for human consumption and the processing removes proteinaceous material, there are no additional toxicity or allergenicity concerns with this product”.

They concluded:

“Health Canada’s review of the information presented in support of the food use of glufosinate herbicide tolerant canola lines MS1 and RF2 concluded that they do not raise concerns related to human food safety. Health Canada is of the opinion that processed oil from MS1, RF2, or hybrids derived therefrom, is as safe and nutritious as that available from current commercial canola varieties. Health Canada’s opinion pertains only to the food use of these glufosinate herbicide tolerant canola lines. Issues related to growing glufosinate herbicide tolerant canola lines, with either male sterility or fertility restoration traits, in Canada and their use as animal feed are addressed separately through existing regulatory processes in the Canadian Food Inspection Agency”.

The EU decision was virtually identical with that for MS1, RF1 PGS1 (123).

19. APPENDIX F

TRANSGENIC OILSEED RAPE HCN92 (= TOPAS 19/2) (AVENTIS CROPSCIENCE).

For a general description of this genetic construct see HCN92 on the University of Nebraska website (124).

The ANZFA conclusions referred to above (119) include this strain.

Health Canada's review of the information presented in support of the food use of refined oil from glufosinate ammonium tolerant canola line HCN92 concluded that such refined oil does not raise concerns related to safety. Health Canada is of the opinion that refined oil from canola line HCN92 is as safe and nutritious as refined oil from current commercial varieties. Health Canada's opinion deals only with the food use of refined oil from the genetically modified canola line HCN92. Issues related to growing canola line HCN92 in Canada and its use as animal feed are addressed separately through existing regulatory processes in the Canadian Food Inspection Agency (125).

In the European Union, the view was expressed thus (126):

"Article 1

1. Without prejudice to other Community legislation, in particular Regulation (EC) No 258/97 of the European Parliament and the Council (4), and subject to paragraph 2 of this Article, consent shall be given by the competent authorities of the United Kingdom to the placing on the market of the following product, notified by AgrEvo UK Crop Protection (Ref. C/UK/95/M5/1): seeds of spring swede rape (***Brassica napus*** L. spp. oleifera) derived from traditional breeding crosses between non-genetically modified swede rape and a line resulting from transformation event Topas 19/2 which has been transformed using plasmid pOCA/AC containing:
   (a) a synthetic ***pat*** gene coding for phosphinothricin acetyltransferase under the regulation of 35S promoter and terminator sequences from cauliflower mosaic virus, and
   (b) an ***npt II*** gene coding for neomycin phosphotransferase II under the regulation of the nopaline synthase promoter and on actopine synthase terminator sequence.
2. The consent shall cover the placing on the market of the product or handling in the environment during import and before and during storage and processing."

Finally, The UK ACNFP wrote (127):

"Substantial Equivalence: Compositional analysis on seed harvested from trials at a number of locations within Canada in several successive years provided data on oil content, fatty acid composition (including erucic acid content) and glucosinolate levels. Those for the seed from the genetically modified plants fall within the range for non-GM control varieties. For food purposes the product is likely to be highly processed so that both the genetic material introduced into the transgenic plant and its protein products would be absent from the refined product.

On the basis of substantial equivalence, it can be concluded that refined products from plants derived from this glufosinate tolerant plant would be safe for food use", followed by:

“Overall Assessment: The Commission requested the Scientific Committee on Plants ‘to consider whether there is any reason to believe that the import of seeds of AgrEvo Glufosinate tolerant GM oilseed rape with the aim of processing is likely to cause any adverse effects on human health and the environment’. In the assessment of the dossier against the criteria set out in Directive 90/220/EEC, the Committee has reached the following conclusion:

The Committee after examining and considering the existing information and data provided in the AgrEvo dossier, against the background of available knowledge in the areas concerned, considers that there is no evidence indicating that the seeds of AgrEvo glufosinate ammonium tolerant genetically modified oilseed rape, to be imported and processed in the manner indicated, are likely to cause adverse effects on human or animal health and the environment.”

20. APPENDIX G

TRANSGENIC SOYBEANS ROUNDUP READY® EVENT GTS 40-3-2 (MONSANTO)

A description of the product can be downloaded from the University of Nebraska website (128); Monsanto's own "Safety Assessment of Roundup Ready® Soybean Event 40-3-2" is available on that company's website (129).

Monsanto's application on herbicide-tolerant soybeans to the UK regulatory authorities was submitted on July 27th, 1994 (130). The document (130 pages of typescript) comprises introduction, conclusion, references, etc. plus three main evidential sections:

1. CP4 EPSPS: The protein conferring glyphosate tolerance to GTS;
2. Information supporting GTS safety specified by category M of the ACNFP decision tree;
3. Confirmatory animal studies supporting the wholesomeness and safety of GTS when used in animal feeds.

Note that this submission was made some three years before the first UK import of GTS.

The European Commission approval came on April 3rd, 1996:

"Article 1

1. Without prejudice to other Community legislation and subject to paragraphs 2 and 3, consent shall be given by the competent authorities of the United Kingdom for the placing on the market of the following product, notified by Monsanto Europe (Ref. C/UK/94/M3/1) under Article 13 of Directive 90/220/EEC.
   The product consists of soya beans derived from a soya bean (***Glycine max*** L. cv A5403) line (40-3-2) in which the following sequences have been inserted:
   a single copy of the gene coding for glyphosate tolerance ***CP4 5*** enolpyruvylshikimate-3-phosphate synthase (CP4 EPSPS) from ***Agrobacterium*** sp. Strain CP4, and the chloroplast transit peptide (CTP) coding sequence from ***Petunia hybrida*** with the promoter P-E35S from cauliflower mosaic virus and the nopaline synthase gene terminator from ***Agrobacterium tumefaciens***.
2. The consent shall cover any progeny derived from crosses of the product with any traditionally red soya bean lines."

The consent shall cover the following uses of the product: handling in the environment during import before and during storage, and before and during its processing to non-viable products." (131).

A number of papers have been published in peer-reviewed journals on the compositional analysis of transgenic soybean and on animal feeding trials (132-134).

21. APPENDIX H

DELAYED-SOFTENING TOMATOES F (ZENECA SEEDS)

For a general description of this construct see B, Da, F on the University of Nebraska website (135). The tomato is modified to produce lower levels of the enzyme polgalacturonase so that the fruit ripens normally but allows a margin of flexibility of harvest by staying at an appropriate ripening stage for a couple of days longer. The result is that better quality fruit can be delivered to the manufacturers for turning into processed food products. Tomato puree produced from these fruits was sold successfully in the UK between 1996 and 1998.

On September 20th, 1994 the FDA reported that "the new varieties contain only one added protein…Zeneca noted that the safety of this protein in the development of new varieties of tomatoes has been addressed previously…Nonetheless, Zeneca presented data to show that the protein was expressed at extremely low levels in fresh tomato fruits and was essentially absent from the processed products due to denaturation and inactivation…Zeneca has concluded, in essence, that the new tomato variety they have developed is not significantly altered within the meaning of 21 CFR 170.30(f)(2) when compared to tomato varieties with a history of safe use. At this time, based on Zeneca's description of its data and analysis, the agency considers Zeneca's consultation on this product to be complete" (136). In response to their petition for a determination of non-regulated status, USDA evaluated scientific data submitted by Zeneca Plant Science and Petoseed Co. Inc. as well as other scientific data and comments received from the public. Having "determined that these tomato lines do not present a plant pest", and in response on June 22, 1995, the U.S. Department of Agriculture ruled it will no longer regulate …..tomato lines designated as B, Da and F, which have been genetically engineered for suppressed polygalacturonase enzyme activity (137).

Health Canada's review of the information presented in support of the food use of reduced polygalacturonase activity tomato hybrids 1401F, H282F, 11013F and 7913F concluded that these hybrids do not raise concerns related to human food safety. Health Canada is of the opinion that the products from tomato hybrids 1401F, H282F, 11013F and 7913F are as safe and nutritious as those available from current commercial tomato cultivars. Health Canada has notified Zeneca Plant Science that it has no objection to the food use of the transgenic tomato hybrids 1401F, H282F, 11013F and 7913F which have been developed to exhibit reduced pectin degradation through a suppression of polygalacturonase activity. The Department conducted a comprehensive assessment of these novel hybrids according to its Guidelines for the Safety Assessment of Novel Foods (September 1994) (138).

The EU Health Scientific Committees Scientific Committee on Plants commented on the safety aspects of these tomatoes:

> "***Potential for Gene Transfer***: The genetically modified tomato contains the antibiotic resistance marker ***nptII***, conferring resistance to neomycin/kanamycin, under the control of nopaline synthase promoter. The company has presented evidence based on PCR techniques that 'hot break processing' used for the preparation of puree denatures and fragments the gene. The limited amount of tomato pomace used as feed for ruminant animals is recovered after such heat processing. Thus the potential for transfer of the ***nptII*** resistance gene to bacteria of the digestive tract of humans or

livestock is essentially zero. In the unlikely event that processing failed or was not applied, it is theoretically possible that this DNA could transform an intestinal bacterium and that recombination could bring the gene under the control of a bacterial promoter. However, even if this occurred, the potential to compromise chemotherapy in humans is negligible. Kanamycin resistant bacteria are relatively common in nature and the introduction of the ***nptII*** gene would not increase the existing risk to humans to any significant extent.

Safety of Gene Products: Heat processing ensures that the enzyme NPTII does not survive in a biologically active form. Regular human consumption of tomato products containing the heat-denatured protein has not caused recognised problems relating to toxicity or allergenicity. Neither effect would have been expected as judged by comparisons of amino acid sequences made with known antigens, the published lack of effects of the intact NPTII protein in chronic toxicity studies in rats and the recorded ease of degradation of this protein in the digestive tract.

Polygalacturonase is a natural component of all food plants. The truncated PG gene present in the construct is identical to the corresponding endogenous tomato gene and thus confers no additional risks."

Accordingly, "The Committee after examining and considering the existing information and data provided in the Zeneca dossier, against the background of available knowledge in the areas concerned, considers that there is no evidence indicating that the production of the processing tomatoes of Zeneca with down-regulated polygalacturonase enzyme and the products derived from the tomatoes and their eventual use as any other processing tomato are likely to cause adverse effects on human or animal health and the environment" (139).

The EU concluded that "Having reviewed all the information provided by the petitioner, and in the light of current published scientific information, it can be concluded that, from the consumer health point of view, processed foods derived from GM tomatoes that are the subject of this application are as safe as products from conventional fruit" (140).

Finally, the recommendation of the UK Advisory Committee on Novel Foods and Processes was that "The UK Competent Authority is of the opinion that the processed products from the GM tomato line TGT7F are as safe for human consumption as non-GM tomato processed products and therefore, provided that no reasoned objections are received within 60 days, that the applicant should be informed that they may place the products on the market" (141).

22. REFERENCES

If Hitler invaded hell I would make at least a favourable reference to the devil in the House of Commons. – Winston Churchill

1. Kuiper, H.A., Kleter, G.A., Noteborn, H.P.J.M and Kok, E.J. (2001). ***Assessment of the food safety issues related to genetically modified foods***. ***The Plant Journal***, **27** (6), 503-528 — http://www.blackwell-science.com/products/journals/plantGM/tpj1119.pdf.

2. Crawley, M.J., Brown, S.L., Hails, R.S., Kohrs, D.D. and Rees, M. (2001). ***Transgenic crops in natural habitats***, ***Nature***, **409**: 682- 683) — http://www.nature.com/cgi-taf/DynaPage.taf?content_filetype=pdf&file=/nature/journal/v409/n6821/full/409682a0_fs.html&_UserReference=C0A804ED46508748353B96191FCF3BE0016D.

3. ***The Great Food Gamble*** — http://www.foe.co.uk/resource/reports/great_food_gamble.pdf

4. The Food Standards Agency's View on GM Food Safety — http://www.foodstandards.gov.uk/farm_fork/gmview.htm

5. ***Safety of Genetically Engineered Crops***, VIB Publication, Flanders Interuniversity Institute for Biotechnology, March 2001 — http://www.vib.be/downloads/bioveiligheidseducatie/report.pdf

6. Editorial Page: ***The Luddites are Coming! The Luddites are Coming***! ***– Those Who Are Blind To The Fruits Of Progress***. ***San Diego Union Tribune***, June 22, 2001.

7. Report of the Inter-Departmental Group on Modern Biotechnology. Stationary Office Dublin (2000) —http://www.entemp.ie/BIOTEC.PDF18

8. Alan McHughen: ***A Consumer's Guide to GM Food: from green genes to red herrings***. Oxford University Press (2000). ISBN 0 19 850714 3 (pbk); in the US Pandora's Picnic Basket ISBN 0 19 850674 0 (hbk)

9. Martina Newell McGloughlin and James I. Burke: ***Biotechnology — present position and future developments***. Teagasc, Ireland (2000). ISBN 1 84170 122X

10. University of California — http://ucbiotech.org/resources/index.html

11. International Food Information Council — http://ificinfo.health.org/press/biobrochure.htm

12. Cabinet Office Genetic Modification (GM) Issues — http://www.cabinet-office.gov.uk/gm-info.

13. Harvey, M.H., McMillan, M., Morgan, M.R. and Chan, H.W. (1985). ***Solanidine is present is sera of healthy individuals and in amounts dependent on their dietary potato consumption***. ***Human Toxicology***, **4**, 187-197.

14. Van Gelder, W.M.J., Vinke, J.H. and Scheffer, J.J.C. (1988). Steroidal glycoalkaloids in tubers and leaves of ***Solanum*** species used in potato breeding. ***Euphytica*** Supplement: 147-158.

15. Coulston, F. and Kolbye, A.C. (1990). ***Biotechnologies and food: assuring the safety of foods produced by genetic modification***. Regulatory Toxicology and Pharmacology, **12**, S1-S196.

16. Beier, R.C. (1990). ***Natural pesticides and bioactive components in food***. ***Reviews of Environmental Contamination and Toxicology***, **113**, 47-137.

17. Ames, B.N. and Gold, L.S. (1999). In ***Fearing Foods***, (ed. by Morris, J. and bate, R.), 18-38. Oxford: Butterworth Heinemann

18. ***Cyberspace healthclinic.co.uk The UK's definitive complementary health web guide Health News*** — http://www.cyberspacehealthclinic.co.uk/health_news/02_July_2001.html#allergy

19. ***MCA publications*** — http://www.mca.gov.uk/inforesources/publications/mcapublic.htm#General%20Publications

20. ***The Rules Governing Medicinal Products in the European Union —*** http://pharmacos.eudra.org/F2/eudralex/index/htm

21. http://www.mca.gov.uk/pilot/pilotintro.htm

22. ***AstraZeneca Annual Report 2000***, page 19 — http://www.astrazeneca.com/AnnualRep2000/annualreportpt1.pdf

23. ***Substantial Equivalence in Food Safety Ass***essment; The Council for Biotechnology Information, March 11, 2001 — http://www.whybiotech.com/en/pressrel/con728.asp?MID=18)

24. ***The principle of substantial equivalence*** — http://www.ncbe.reading.ac.uk/NCBE/GMFOOD/subequiv.html

25. ***Biotechnology and Food Safety Report of a Joint FAO/WHO Consultation*** — http://www.fao.org/WAICENT/faoinfo/economic/esn/biotech/conclude.htm

26. Millstone, E., Brunner, E. and Mayer, S. ***Beyond "substantial equivalence"***. ***Nature***, (October 7, 1999) — http://members.tripod.com/~ngin/se.htm

27. ***The Recombinant DNA Debate*** — http://www.ndsu.nodak.edu/instruct/mcclean/plsc431/debate/debate3.htm

28. ***Agricultural Biotechnology, US Department of Agriculture*** — http://www.aphis.usda.gov/biotech

29. BSS Biosafety Library — http://www.aphis.usda.gov/biotech/biosafe.html

30. ***United States Regulatory Oversight in Biotechnology Responsible Agencies – Overview*** — http://www.aphis.usda.gov/biotech/OECD/usregs.htm

31. ***FDA'S Policy for Foods Developed by Biotechnology*** — http://vm.cfsan.fda.gov/~lrd/biopolcy.html#

32. AFDO Conference, June 19, 2000 — http://vm.cfsan.fda.gov/~comm/afdo2k.html

33. ***Premarket Notice Concerning Bioengineered Foods*** — http://vm.cfsan.fda.gov/~lrd/fr010118.html

34. ***FDA Announces Proposal and Draft Guidance for Food Developed Through Biotechnology*** — http://www.cfsan.fda.gov/~lrd/hhbioen3.html

35. ***Bioengineered Foods: Will They Cause Allergic Reactions***? — http://www.cfsan.fda.gov/~dms/pubalrgy.html

36. ***Bt Plant-Incorporated Protectants October 15, 2001 Biopesticides Registration Action Document – Bacillus thuringiensis (Bt) Plant-Incorporated Protectants*** — http://www.epa.gov/pesticides/biopesticides/otherdocs/bt_brad2/1overview.pdf

37. ***Bt Plant-Incorporated Protectants October 15, 2001 Biopesticides Registration Action Document II Science Assessment*** — http://www.epa.gov/pesticides/biopesticides/otherdocs/bt_brad2/2%20id_health.pdf

38. Agriculture and Biotechnology Strategies (Canada) Inc.: ***The safety of GM feeds*** — http://64.26.172.90/agbios/gmfeeds.php#2

39. ***Evaluation of the U.S. Regulatory Process for Crops Developed Through Biotechnology, Issue Paper No. 19, October 2001*** — http://www.cast-science.org/pubs/cropregulation.pdf

40. ***IFT Expert Report on Biotechnology and Foods Human Food Safety; Evaluation of rDNA Biotechnology-Derived Foods.*** Food Technology, vol. 54, no. 9, September 2000 — http://www.ift.org/resource/pdf_files/iftreport_safety.pdf

41. ***7th Report Regulation of the United Kingdom Biotechnology Industry and Global Competitiveness [HL 80, 80-I & 80-II]***,1993 — http://www.parliament.the-stationery-office.co.uk/pa/ld199899/ldselect/ldeucom/11/8121506.htm#n55

42. ***Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients —*** http://biosafety.ihe.be/GB/Dir.Eur.GB/FF/258_97/258_97.html

43. ***Facts on GMOs in the EU*** — http://europa.eu.int/comm/dgs/health_consumer/library/press/press63_en.pdf

44. ***Questions and Answers on the regulation of GMOs in the EU*** (Memo 00277, 24 July 2001 — http://www.agbios.com/articles/memo00277.pdf

45. 8.11.2000 COM(2000) 716 final 2000/0286 (COD) ***Proposal for a Regulation of the European Parliament and of the Council laying down the general principles and requirements of food law, establishing the European Food Authority, and laying down*** procedures in matters of food — http://64.26.172.90/docroot/decdocs/bnfM034.pdf);

46. 25.7.2001 COM(2001) 425 final 2001/0173 (COD) ***Proposal for a Regulation of the European Parliament and of the Council on genetically modified food and feed*** — http://www.foodstandards.gov.uk/pdf_files/consultations/gm_foodfeed.pdf;

47. Working Document of the Services of the Commission (not yet approved by the Commission) SANCO/1773/2001 ***Proposal for a Regulation of the European Parliament and of the Council on genetically modified food and feed —*** http://www.foodstandards.gov.uk/pdf_files/gmregs.pdf

48. ***Placing genetically modified foods (GM foods) on the EU Market*** revised to 27/04/2001 — http://biosafety.ihe.be/NF/Gmfoods/Gmfood_market.html;

49. ***Placing transgenic crops on the EU market*** — http://biosafety.ihe.be/TP/Tpmarket.html

50. ***Products applied for and approved in the EU to be placed on the market according to directive 90/220/EEC —*** http://www.rki.de/GENTEC/INVERKEHR/INVKLIST_E.HTM

51. ***EC-sponsored research of safety of genetically modified organisms*** [especially articles in Chapter 4, ***Food — tackling food safety concerns over GMOs*** (2001) — http://europa.eu.int/comm/research/quality-of-life.gmo

52. ***EU safety regulation of genetically-modified crops*** from the Open University (to be published in a special issue of the ***Journal of Risk Research*** (2000) and available at http://www-tec.open.ac.uk/cts/bpg.htm

53. ***EU-level report Safety Regulation of Transgenic Crops: Completing the Internal Market? A study of the implementation of EC Directive 90/220*** .

54. ***Communication from the Commission: Towards a Strategic Vision of Life Sciences and Biotechnology: Consultation Document —*** http://europa.eu.int/comm/biotechnology/pdf/doc_en.pdf

55. Advisory Committee on Novel Foods and Processes Home Page http://www.foodstandards.gov.uk/committees/acnfp/acnfphp.htm

56. Food Standards Agency Home Page — http://www.foodstandards.gov.uk/your_food.htm)

57. ***Guidance Notes — Novel foods and novel food ingredients legislation*** — http://www.foodstandards.gov.uk/maff/archive/food/novel/gnnovel.htm#11b

58. ***ACNFP Committee Members*** — http://www.foodstandards.gov.uk/maff/pdf/memb6.pdf

59. ***Statistically Valid Data to Support Applications for Safety Clearance of Crop Products under EC Regulation on Novel Foods and Novel Food Ingredients 258/9***7 — http://www.foodstandards.gov.uk/maff/archive/food/novel/stats.htm

60. ***Consideration of the use of human studies in the pre-market safety assessment of novel foods —*** http://www.foodstandards.gov.uk/pdf_files/taste_annb.pdf

61. Toxicological assessment of novel (including GM) foods — http://www.foodstandards.gov.uk/maff/archive/food/novel/toxrev.htm

62. ***The Food Standards Agency's View on GM Food Safety*** — http://www.foodstandards.gov.uk/farm_fork/gmview.htm

63. ***Genetic modification of food fact sheet*** — http://www.foodstandards.gov.uk/farm_fork/gm_factsheet.htm#the

64. ***Health and Environmental Risks of Genetically Modified Soya — Food Safety Issues Considered by the ACNFP*** — http://www.foodstandards.gov.uk/maff/archive/food/novel/issues.htm

65. http://www.foodstandards.gov.uk/committees/acnfp/newapp.htm#guide

66. ***List of Applications for approval of Novel (inc. GM) Foods & Novel Processes*** — http://www.foodstandards.gov.uk/committees/acnfp/pq585att.htm).

67. ***Draft final risk analysis report/application a386/food derived from the insect-protected, herbicide-tolerant Bt-11 corn —*** http://www.anzfa.gov.au/_srcfiles/A386IR.pdf

68. ***Final risk analysis report/application a385/food derived from the insect-protected Bt-176 corn*** — http://www.anzfa.gov.au/_srcfiles/A3851R.pdf

69. ***Regulation of GM Foods***. Australian New Zealand Food Authority — http://www.biotechnology.gov.au/Primary_Producers/Rural_Forum_Info/Launceston/GalwayLaunceston.ppt

70. ***The safety of GM feeds*** — http://64.26.172.90/unl2/gmfeeds.php

71. Document 1.1 ***Substantial equivalence Maize*** — http://www.europabio.org/upload/articles/article_104.pdf

72. Document 1.4 ***Substantial equivalence Soybean issue 1*** — http://www.europabio.org/upload/articles/article_102.pdf

73. Food Law News - UK - 200017 May 2000: ***GM FOOD - Presence of Genetically Modified Crop in UK Presents No Human Health Risk Says Chairman*** -- http://www.fst.rdg.ac.uk/foodlaw/news/uk-00-36.htm

74. Health Canada ***Assessment: - Novel Food Information Food Biotechnology Glyphosate Tolerant Canola GT73*** -- http://www.biotechbasics.com/product_information/rr_canola_health.html

75. Health Canada Assessment: - Health Canada Assessment: - ***Novel Food Information Food Biotechnology High Lauric Acid Lines 23-198, 23-18-17*** -- http://www.biotechbasics.com/product_information/hl_canola_health.html

76. Health Canada Assessment: - ***Novel Food Information Food Biotechnology Insect Resistant Cotton Lines 531 and 757 --*** http://www.biotechbasics.com/product_information/bollgard_cotton_health.html

77. GMOs: ***Spectrum's Commitment to Consumers*** -- http://www.spectrumnaturals.com/gmos.html

78. Agrifood Awareness Australia, Paper 14 ***GM canola, pollen, bees and honey*** -- http://www.afaa.com.au/pdf/14-GM_Canola_bees_and_honey.pdf

79. American Medical Association food biotechnology media briefing — http:// www.ama-assn.org/ama/pub/article/4197-5322.htm

80. Donaldson and May: ***Health implications of genetically modified foods*** — http://www.doh.gov.uk/pub/docs/doh/gmfood.pdf

81. ***Development of new methods for safety evaluation of transgenic food cr***ops — http://europa.eu.int/comm/research/quality-of-life/gmo/04-food/04-05-project.html) including the foreword — http://europa.eu.int/comm/research/quality-of-life/gmo/general-intro.html

82. Cahagnier, B and Melcion, D. ***"Mycotoxines de Fusarium dans les mais-grains a la recolte; relation entre la presence d'insectes (pyrale, sesamie) et la teneur en mycotoxines"*** Proceedings of the 6th International Feed Conference, Food Safety: current situation and perspectives in the European Community. Piacenza, Italy (ed. by G. Piva, F. Masoero) 27-28 November, 2000. pp.237-249.

83. Dowd, P (2000). ***"Indirect Reduction of Era Molds and associated Mycotoxins in Bacillus thuringiensis Corn Under Controlled and Open Field Conditions: Utility and Limitations"***. ***Journal of Economic Entomology***" **93**:1669-1679.

84. ***Report of the OECD workshop on the toxicological and nutritional testing of novel foods***. — http://www1.oecd.org/ehs/ehsmono/aussoidrEN.pdf

85. ***Evaluation of Allergenicity of Genetically Modified Food***s http://www.fao.org/waicent/faoinfo/economic/ESN/gm/allergygm.pdf

86. ***Safety aspects of genetically modified foods of plant origin*** http://www.who.int/fsf/GMfood/FAO-WHO_Consultation_report_2000.pdf).

87. Ames, B.N., Profet, M. and Gold, L.S. (1990). ***Dietary pesticides***. ***Proceedings of the. National. Academy of Sciences of the U.S.***, **87**, 7777-7781.

88. Morris, J., ed. (2000). ***Rethinking Risk and the Precautionary Principle.*** Oxford: Butterworth-Heinemann.

89. Address by David Byrne on the ***Precautionary Principle in the domain of human health and food safety*** atThe Economist Conferences "Colloque sur le principe de Précaution organisé par The Economist avec la collaboration de l'Institut Servier", Venue: Salon Dauphine, Place Maréchal De Lattre de Tassigny, 75016 Paris, 1.30pm – 9th November, 2000 — http://europa.eu.int/comm/dgs/health_consumer/library/speeches/speech66_en.html

90. ***Communication from the Commission on the precautionary principle***, 02.02.2000 COM(2000(1) — http://europa.eu.int/comm/dgs/health_consumer/library/pub/pub07_en.pdf

91. http://64.26.172.90/unl2/dbase.php?action=ShowProd&data=BT11+%28X4334CBR%2C+X4734CBR%29&frmat=LONG

92. This document is available from Sheena Bethell, Syngenta Seeds WRO-1004.8.28, Postfach 4002. Basel, Switzerland

93. ***Novel food information – food biotechnology; Insect resistant and herbicide tolerant corn, Bt11 —*** http://64.26.172.90/docroot/decdocs/ofb-096-228-b.pdf

94. ***Decision Document DD96-12: determination of environmental safety of Northrup King Sees' European Corn Borer (ECB) resistant corn (Zea mays L.)*** — http://www.inspection.gc.ca/english/plaveg/pbo/dd9612e.shtml

95. ***Draft final risk analysis report/application a386/food derived from the insect-protected, herbicide-tolerant Bt-11 corn —*** http://www.anzfa.gov.au/_srcfiles/A386IR.pdf

96. ***ANZFA Sixty-Seventh Meeting Canberra 21-22 February 2001 Summary of key outcomes Recommendations relating to Food Standards matters*** — http://www.anzfa.gov.au/aboutanzfa/boardoutcomes/anzfa67.cfm

97. ***Note to File (BNF0017), May 22, 1996*** — http://www.cfsan.fda.gov/~acrobat2/bnfM017.pdf

98. ***Office of Pesticide Programs Biopesticide Fact Sheet Bacillus thuringiensis Cry1Ab Delta-Endotoxin and the Genetic Material Necessary for Its Production (Plasmid Vector pZO1502) in Corn [Bt11] —*** http://www.epa.gov/oppbppd1/biopesticides/factsheets/fs006444t.htm

99. ***398D0292 98/292/EC: Commission Decision of 22 April 1998 concerning the placing on the market of genetically modified maize (Zea mays L. line Bt-11), pursuant to Council Directive 90/220/EEC (Text with EEA relevance)*** — http://europa.eu.int/eur-lex/en/lif/dat/1998/en_398D0292.html

100. ***Bt11-maize [pZO1502]: Assessment of safety for the consumer, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients*** — http://www.gr.nl/engels/welcome/frameset.htm, select “Search” and enter “Bt11”; then click on “Reports published by the Health Council” and click again on “27 April 2000 Bt11-maize [pZO1502]”

101. http://64.26.172.90/unl2/dbase.php?action=ShowProd&data=176&frmat=LONG

102. This document is available from Sheena Bethell, Syngenta Seeds WRO-1004.8.28, Postfach 4002. Basel, Switzerland.

103. ***Final risk analysis report/application a385/food derived from the insect-protected Bt-176 corn*** — http://www.anzfa.gov.au/_srcfiles/A3851R.pdf

104. ***ANZFA Sixty-Seventh Meeting Canberra 21-22 February 2001 Summary of key outcomes Recommendations relating to Food Standards matters*** — http://www.anzfa.gov.au/aboutanzfa/boardoutcomes/anzfa67.cfm

105. ***Note to the File; Subject: Bt-Resistant Corn*** — http://www.cfsan.fda.gov/~acrobat2/bnfM024.pdf

106. ***Novel food information – food biotechnology; Insect resistant and herbicide tolerant corn, Bt11 —*** http://64.26.172.90/docroot/decdocs/ofb-095-353-a.pdf

107. ***Decision Document DD96-09: Determination of Environmental Safety of Event 176 Bt Corn (Zea mays L.) Developed by Ciba Seeds and Mycogen Corporation*** — http://www.inspection.gc.ca/english/plaveg/pbo/dd9609e.shtml

108. http://europa.eu.int/eur-lex/en/lif/dat/1997/en_397D0098.html

109. ***397D0098 97/98/EC: Commission Decision of 23 January 1997 concerning the placing on the market of genetically modified maize (Zea mays L.) with the combined modification for insecticidal properties conferred by the Bt-endotoxin gene and increased tolerance to the herbicide glufosinate ammonium pursuant to Council Directive 90/220/EEC (Text with EEA relevance)*** — http://europa.eu.int/comm/food/fs/sc/scp/out78_gmo_en.html

110. Brake, J. and Vlachos. D. (1998). ***Evaluation of Transgenic Event 176 ‘Bt’ Corn in Broiler Chickens. Poultry Science***, 77, 648

111. ***Office of Pesticide Programs Biopesticide Fact Sheet Bacillus thuringiensis Cry1Ab Delta-Endotoxin and the Genetic Material Necessary for Its Production (Plasmid Vector pCIB4431) in Corn [Event 176]*** —
http://www.epa.gov/oppbppd1/biopesticides/factsheets/fs006458t.htm

112. http://64.26.172.90/unl2/dbase.php?action=ShowProd&data=MON810

113. http://www.monsanto.com/monsanto/about_us/monsanto_pledge/transparency/pss_yieldgardcorn.html

114. ***YieldGard® Corn – Insect Protection*** —
http://www.monsanto.com/monsanto/about_us/monsanto_pledge/transparency/yieldgardcorn_product.pdf

115. ***Health Canada Assessment Novel Food Information – Food Biotechnology Insect Resistant Corn, MON 810 June, 1997*** —
http://www.biotechbasics.com/product_information/yg_corn_health.html

116. ***EU: Opinion of the Scientific Committee on Plants Regarding the Genetically Modified, Insect Resistant Maize Lines Notified by the Monsanto Company:***
http://europa.eu.int/comm/food/fs/sc/scp/out02_en.html

117. 398D029498/294/EC: ***Commission Decision of 22 April 1998 concerning the placing on the market of genetically modified maize (Zea mays L. line MON 810), pursuant to Council Directive 90/220/EEC*** (Text with EEA relevance): http://europa.eu.int/eur-lex/en/lif/dat/1998/en_398D0294.html)

118. MS1, RF1 =>PGS1 —
http://64.26.172.90/unl2/dbase.php?action=ShowProd&data=MS1%2C+RF2+%3D%3EPGS2&frmat=LONG

119. ***DRAFT RISK ANALYSIS REPORT, APPLICATION A372: Oil derived from glufosinate-ammonium tolerant canola lines Topas 19/2 and T45 and Oil derived from glufosinate-ammonium tolerant and pollination controlled lines Ms1, Ms8, Rf1, Rf2 and Rf3*** —
http://www.anzfa.gov.au/_srcfiles/A372FAR.pdf

120. ***396D0158 96/158/EC: Commission Decision of 6 February 1996 concerning the placing on the market of a product consisting of a genetically modified organism, hybrid herbicide-tolerant swede-rape seeds (Brassica napus L. oleifera Metzq. MS1Bn • RF1Bn), pursuant to Council Directive 90/220/EEC (Text with EEA relevance)***
Official journal NO. L 037 , 15/02/1996 P. 0030 - 0031 —
http://64.26.172.90/docroot/decdocs/01-290-012.pdf

121. MS1, RF2 =>PGS2 —
http://64.26.172.90/unl2/dbase.php?action=ShowProd&data=MS1%2C+RF2+%3D%3EPGS2&frmat=LONG

122. FD/OFB-095-229-A NOVEL FOOD INFORMATION - FOOD BIOTECHNOLOGY POLLINATION CONTROL SYSTEM FOR CANOLA, MS1/RF2— http://64.26.172.90/docroot/decdocs/ofb-095-229-a.pdf

123. ***Community legislation in force 397D0393 97/393/EC: Commission Decision of 6 June 1997 concerning the placing on the market of genetically modified swede- rape (Brassica napus L. oleifera Metzg. MS1, RF2), pursuant to Council Directive 90/220/EEC (Text with EEA relevance) Official journal NO. L 164 , 21/06/1997 P. 0040 - 0041*** — http://64.26.172.90/docroot/decdocs/01-290-013.pdf

124. HCN92 —http://64.26.172.90/unl2/dbase.php?action=ShowProd&data=HCN92

125. ***Novel Food Information - Food Glufosinate Ammonium Tolerant Canola (HCN92)*** — http://64.26.172.90/docroot/decdocs/2001109-A.pdf

126. ***398D0291 98/291/EC: Commission Decision of 22 April 1998 concerning the placing on the market of genetically modified spring swede rape (Brassica napus L. ssp. oleifera), pursuant to Council Directive 90/220/EEC (Text with EEA relevance)*** Official Journal L 131 , 05/05/1998 p. 0026 - 0027 — http://64.26.172.90/docroot/decdocs/01-290-003.pdf

127. ***Opinion of the Scientific Committee on Plants Regarding the Genetically Modified, Glufosinate-Tolerant Rape Notified by the Agrevo Company (NOTIFICATION C/UK/95/M5/1)*** — http://64.26.172.90/docroot/decdocs/01-290-002.pdf

128. http://64.26.172.90/unl2/dbase.php?action=ShowProd&data=GTS+40-3-2&frmat=LONG

129. ***Safety assessment of Roundup Ready® Soybean Event 40-3-2*** — http://www.monsanto.com/monsanto/about_us/monsanto_pledge/transparency/roundupsoy_product.pdf

130. Padgette, S. R., et al. (1994) ***Application to the United Kingdom Advisory Committee on Novel Foods and Processes for The Review of the Safety of Glyphosphate Tolerant Soybeans by Stephen P. Waters,*** The Agricultural Group of Monsanto Company, Monsanto Europe, Brussels — British Library Document Supply Centre, Boston Spa, Wetherby LS23 7BQ, quoting 'sup' number: 110 93, shelfmark no. 0713.369

131. EU: 396D0281 – 96/281/EC: ***Commission Decision of 3 April 1996 concerning the placing on the market of genetically modified soya beans (Glycine max L.) with increased tolerance to the herbicide glyphosate, pursuant to Council Directive 90/220/EEC*** (Text with EEA relevance) Official journal NO. L 107 , 30/04/1996 P. 0010 – 0011: http://europa.eu.int/eur-lex/en/lif/dat/1996/en_396D0281.html

132. Padgette S. et al. (1996). The composition of glyphosate tolerant soybean seeds is equivalent to that of conventional soybeans. ***Journal of Nutrition***, **126**, 707-16. An abstract of this paper is available at http://www.monsanto.com/monsanto/biotechnology/background_information/99june23_composition.html

133. Harrison, L.A., M.R. Bailey, M. Naylor, J. Ream, B. Hammond, D.L. Nida, B. Burnette, T.E. Nickson, T. Mitsky, M.L. Taylor, R.L. Fuchs and S.R. Padgette (1996). ***The expressed protein in glyphosate-tolerance soybean, 5-enolpryruvyl-shikimate-3-phosphate synthase from Agrobacterium sp. strain CP4, is rapidly digested in vitro and is not toxic to acutely gavaged mice***. ***Journal of Nutrition***, **126**, 728-740.

134. Hammond B., J. Vicini, G. Hartnell, M.W. Naylor, C.D. Knight, E. Robinson, R. L. Fuchs, and S.R. Padgette (1996). ***The feeding value of soybeans fed to rats, chickens, catfish and dairy cattle is not altered by genetic incorporation of glyphosate tolerance***. ***Journal of Nutrition***, **126**, 717-727. An abstract of this paper is available both at http://www.indianasoybeanboard.com/Genetically.html and http://dragon.zoo.utoronto.ca/~jlm-gmf/T0701A/cfish.html

135. http://64.26.172.90/unl2/dbase.php?action=ShowProd&data=B%2C+Da%2C+F&frmat=LONG).

136. ***Processing tomatoes having suppressed polygalacturonase (PG) activity*** — http://64.26.172.90/docroot/decdocs/bnfM003.pdf

137. ***USDA Rules on Genetically Engineered Tomato Lines —*** http://www.aphis.usda.gov/pa/press/1995/06/d95-0162.txt; Extract from the ***Federal Register*** — http://www.epa.gov/docs/fedrgstr/EPA-IMPACT/1995/June/Day-23/pr-1027.html

138. ***Suppressed Polygalacturonase Activity Tomato Hybrids, 1401f, H282f, 11013f, 7913f*** — http://64.26.172.90/docroot/decdocs/ofb-096-180-a.pdf

139. ***Opinion of the Scientific Committee on Plants regarding submission for placing on the market under directive 90/220/EEC of genetically modified processing tomato line TGT7F notified by Zeneca (notification C/ES/96/01)*** (Opinion of the Scientific Committee on Plants expressed on 23 June 1998) — http://europa.eu.int/comm/food/fs/sc/scp/out19_en.html

140. European Commission Health & Consumer Protection Directorate-General Directorate B – Scientific Health Opinions Unit B3 – Management of scientific committees II Scientific Committee on Food SCF/CS/NF/TOM/6 REV 4 final 04/10/99 – ***Opinion on a request for consent to place on the market a tomato fruit genetically modified to down-regulate the production of polygalacturonase (PG), and solely intended for processing*** (expressed on 23/9/99) — http://64.26.172.90/docroot/decdocs/out42_en.pdf

141. Regulation (EC) No 258/97 Application Number 98/UK/1 UK Competent Authority: Initial Assessment Report Competent Food Assessment Body: Advisory Committee on Novel Foods And Processes Report on ***The Safety Assessment of Processed Products from Zeneca's Genetically Modified (GM) Tomatoes Derived from Line Tgt7f*** — http://64.26.172.90/docroot/decdocs/tgt7f_acnfp.pdf