GM SCIENCE REVIEW

FIRST REPORT

An open review of the science relevant to GM crops and food based on the interests and concerns of the public

PREPARED BY THE GM SCIENCE REVIEW PANEL (JULY 2003)

Chapter 1

GENERAL INTRODUCTION

1.1 WHY HAVE A SCIENCE REVIEW?

Developments in science and technology invariably provide society with new opportunities, but also new challenges to apply them responsibly. As with many new technologies, people are keen to embrace many benefits but are concerned about the potential risks. The science of genetics[1] has developed considerably over recent decades, so that we can now fully understand the genetic make-up of many organisms and genetically modify crops and other living things in new ways. The UK is now at a crossroads about whether or not to accept the growing of genetically modified crops in agriculture. The aim of this review is to consider the evidence for both the real and perceived risks and benefits of GM crops from a scientific perspective. Before saying more about the nature of the review it is important to give some background.

In a sense, people have been genetically modifying plants (and many other living things) for thousands of years by breeding and selecting improved plants and by the domestication[2] of crops. Originally, this selection was done without any knowledge of the science of genetics. In the mid-1800s the monk, Gregor Mendel, working on peas established the basic laws of inheritance. In the early 1900s advances in the science of genetics led to a dramatic increase in our understanding of growth, development and inheritance in microbes, plants and animals.

Genes are made of the substance DNA[3]. The structure of DNA was worked out 50 years ago, and since then there have been dramatic advances in the subject of genetics. Working out the structure of DNA[4] was one of the most significant advances in genetics because it gave much better insights into both the structure of genes and how they work. These advances have already had profound impacts on our understanding of the fundamental processes of living things.

Throughout the mid-1900s there were important developments in the application of genetics for plant breeding and crop improvement. A wide range of plant breeding methods[5] has been used to contribute to a substantial increase in crop yields and food production, quality and safety across the world (e.g. the Green Revolution of the 1960s and 1970s in India which has been estimated to have fed over 1 billion extra people from the same area of land). Over the past 30 years, geneticists and plant breeders have been able to isolate and sequence DNA from different living organisms and to insert one or more specific genes into a wide range of important crop plants, worldwide. This new form of *genetic modification* (GM) presents opportunities to modify crops

[1] Genetics is the scientific study of heredity (how characters are passed on from parents to their offspring) and how genes control the development and behaviour of all living things.
[2] Domestication of crops involves selection by people of plants better able to provide food for people, feed for animals, materials for building and making things and medicines for treating illness.
[3] Deoxyribonucleic acid.
[4] Watson and Crick elucidated the structure of DNA at the University of Cambridge in 1953.
[5] The gradual evolution of plant breeding methods will be discussed further in Chapter 4.

in different ways, to make them resist pests and diseases, be more tolerant of drought and other stressful environments, and even produce vaccines and new medicines[6].

The ability to move specific pieces of DNA and genes into crops from different classes of living organisms has, in some countries, led to the widespread use of genetic modification in plant breeding and the extensive cultivation of the crops so produced (see Box 1.1). But there have been reservations and concerns expressed in the UK and in Europe about the possible impacts of cultivation and consumption of GM foods.

As genetic modification raises issues of significant public interest, Mrs Beckett the Environment Secretary announced, on 31st May 2002, that the Government would promote a public debate[7] on the future use of genetically modified organisms (GMOs) in the UK. She also announced two further strands of activity: a study into the costs and benefits[8] associated with growing or not growing GM crops, and a review of the science underpinning the GM assessment and approval process in the UK.

1.2 WHAT HAS THE SCIENCE REVIEW INVOLVED?

The science review, along with the economics and public debate, marks a new venture in public engagement in the UK. The science review has involved taking popular concerns and questions about GM crops and foods and considering the evidence for the salient scientific issues they raise. The issues considered were identified from several activities including a series of public workshops to determine views about GM crops[9]; the public meetings held in association with the Science Review; the Science Review website[10]; and topics highlighted by the Science Review Panel itself. Where possible we have tried to adhere closely to concerns and questions in the way the public have expressed them. The concerns and questions have been grouped into seventeen scientific issues. These issues have then been grouped into four Chapters in the review.

It is important to note that the review is not intended to cover all scientific issues relevant to the assessment of GM crops and foods. For over a decade several independent Government advisory bodies[11] have considered the underlying science relating to production and use of GMOs in their

[6] Examples of research on a wide range of crop genetic modification is summarised in Chapter 6.7 on Horizon Scanning.

[7] The Public Debate is a programme of deliberation with issues for debate framed by the public and conducted at arms length from Government by an independent Steering Board that will report to Government in September 2003. Its focus will be on public views, particularly at grass roots level, to inform Government decision-making. http://www.gmnation.org.uk

[8] An analysis by The Prime Minister's Strategy Unit (SU) of the nature and distribution of costs and benefits that could arise under different scenarios with or without the commercialisation of GM crops in the UK. The SU report was published in July 2003. http://www.number10.gov.uk/output/Page4131.asp

[9] The Foundation Workshops were run independently by Corr Willbourn in the early stages of the Public Debate to establish the principal concerns and questions raised by members of the real public randomly selected. A copy of the Report can be found on the GM Science Review website.

[10] GM Science Review website: http://www.gmsciencedebate.org.uk

[11] The main statutory advisory Committees are the Advisory Committee on Releases to the Environment (ACRE); The Advisory Committee on Novel Foods and Processes (ACNFP) and the Advisory Committee on Animal Feedstuffs (ACAF).

statutory risk assessments on food, feed and environmental matters. There have also been extensive and numerous research programmes to assess the possible risks, benefits and characteristics of GM crops in the UK, EU and worldwide for almost two decades. We have deliberately concentrated on those issues raised that are of particular concern to the public. We have endeavoured to analyse scientific knowledge relevant to those concerns, to acknowledge where there are gaps in scientific understanding, and how these gaps can be dealt with in decision-making and in defining further research. We have also considered what lessons can be learned from comparisons with so-called conventional plant breeding and modern agricultural practice.

While this Science Review is principally designed to aid Government decision-making in the UK, it is acknowledged that any decisions on the future cultivation of GM crops in the UK will be noted across the world, including in developing countries. With the current extent of international trade in a wide range of crops, agriculture in one country frequently impacts on other countries. The work of the economics strand, carried out by the Strategy Unit, has focussed some of its analysis on the ways in which the UK and EU decision on GM crops could impact on decision-making in developing countries. The Science Review Panel felt it important that all countries, including developing countries[12], should carry out their own independent evaluation of the cultivation of particular GM crops; not least because the demands of agriculture, and the societies it supports, vary too much across the world to be able to reach simple generalisations. It is clear that GM technology does offer new approaches to old problems in some agricultural systems, and these have been adopted in some parts of the developing world (Garg *et al.*, 2002; Huang *et al.*, 2002; Pray *et al.*, 2002; Pretty, 2002; Conway, 2003; Nuffield Council on Bioethics, 2003). However, non-GM approaches have also been pointed-out that might also be used as alternatives (AEBC, 2002; Nuffield Council on Bioethics, 2003).

The Science Review process has been open and accessible to the public in various ways through: a dedicated website[13], through public Science Review meetings, and through public attendance at Science Review Panel meetings[14].

Discussions during the Science Review process have suggested that while practising research scientists are familiar with how scientific knowledge is acquired, communicated and validated; there is far less familiarity of these processes in the wider community. We thought it would be helpful, therefore, first to give the reader some insights into the scientific process.

1.3 HOW IS SCIENTIFIC KNOWLEDGE ACQUIRED?

Scientists are usually people who are fascinated by learning about how things work. Plant biologists are interested in how plants grow and develop, resist pests and diseases, produce many different products and compete with other plants. They are often intrigued by how plant species

[12] The role of GM crops in developing countries was raised in the Corr Willbourn Foundation Workshops and in contributions to the Science Review website.
[13] GM Science Review website: http://www.gmsciencedebate.org.uk
[14] The public was invited to observe all full Science Review Panel meetings. The first set of drafting subgroup discussions was without the public, but later the public was invited to observe.

have evolved and how plants can be selected for different purposes (food, feed, health, energy, raw materials etc). Interest in how things work has existed for as long as humankind has been evolving. Particularly during the past two centuries or so, people have engaged in scientific observation and experimentation on an expanding scale. This has led to significant changes in society. Most, but certainly not all these changes could be described as beneficial. For instance, 150 years ago average human life expectancy was around 40 years, it is now close to 80 years. Science, in its various forms has undoubtedly made a significant contribution to this change.

The development of scientific knowledge is affected not only by the interests of individual scientists, but also by the allocation of resources to research. This reflects complex economic and institutional issues and raises questions of priorities and the distribution of benefits and risks. Where there are uncertainties, these may often be open to legitimately divergent interpretations. Such scientific judgements on uncertainty may in turn be informed by wider social and economic perspectives. For instance, modern intensive farming methods have yielded many economic benefits but have, also been linked to a decline in certain forms of wildlife. Science and technology cause environmental damage and it is our wish to understand the risk of damage from new developments.

Over the past two centuries, international science has evolved a set of working principles based on the accumulation of evidence, assessment of that evidence and communication by publication, so that the global scientific community can benefit from shared knowledge. A fundamental part of the assessment of science is peer review by fellow scientists with relevant and complementary experience and expertise. Over this time, there has also been an evolution in the formal methods of the scrutiny of scientific evidence to provide the so-called ‘scientific method’ we have today.

The process can be illustrated as follows. A scientist, interested in how a particular plant is able to resist a disease, studies various features of the disease and the way the plant avoids or actively resists infection. In modern science this usually involves carrying out experiments to answer certain questions about the disease-causing microbe and the plant host. Eventually the scientist will develop a hypothesis to explain the evidence observed. A hypothesis (or model) is often used because it helps to identify the gaps in knowledge and the questions to be answered by further research. Experiments to find information to fill these gaps are then designed and carried out. Proper controls and statistically valid results are critical. Scientists frequently communicate with colleagues during the course of the investigation to learn from their experience. Eventually when they have gathered a sufficient amount of new knowledge about the subject they decide to publish the results.

A report on the research is then prepared as a scientific paper and sent to a Journal specialising in relevant areas of science (e.g. plant diseases). The Journal editor sends the paper out to fellow scientists or referees (usually anonymously) for comment. Peer reviewers’ comments are then communicated back to the author who must modify the paper accordingly or provide a convincing justification why not, before the scientific paper can be published. Scientists new to the peer review process often find it unnecessarily critical and negative. But peer review and the refereeing process are vitally important for the evidence-based evolution of scientific knowledge. The scientific method we currently have is by no means infallible, not least because we can never know ‘everything about everything’; but it is an approach that has stood the test of time, is objective and is the best method we have.

In this science review we agreed at the outset that we would rely principally on evidence from refereed publications that have passed through a rigorous peer review process. However we also agreed that scientific evidence from conference proceedings, specialised technical reports and other publications that have not gone through a comparable peer review may also contain information valuable to the review process. We have peer reviewed this non-peer reviewed literature ourselves and selected what we think is reasonable. The quality of the evidence surrounding GM crops varies considerably. Some claims amount to speculation or cold propaganda, with no underpinning scientific evidence; others are well supported by sound scientific evidence. Sometimes the conclusions of scientific evidence are contradictory or inconclusive. In these instances we have examined the evidence, argued the points and reached conclusions based on the best scientific evidence available. In several instances we have identified significant gaps in knowledge and discussed how they might be dealt with. It is accepted that science can never prove that something cannot/will not ever happen or does not exist, and it is thus unreasonable to demand that it can or should.

1.4 WHO HAS BEEN INVOLVED IN THE REVIEW?

Many people have participated in the review in different ways. Members of the public who participated in the Public Debate Foundation Workshops[15] helped to identify the principal questions and concerns that are the focus of this scientific review. Similarly people who participated in the public meetings of the Science Review and responded to the dedicated website also helped to identify the salient scientific issues.

The review has been carried out by an independent Scientific Review Panel drawing on 24 experts in natural and social sciences with a broad range of relevant and complementary expertise. The Panel was chaired by Professor Sir David King[16] working with Professor Howard Dalton[17]. Various people on the Panel carried out the role of authorship on papers in the early phases of the review, this evolved into an editorship role as panel members interacted and exchanged views and finally the secretariat took on the role of mediator. At the last meeting we all progressed in such a way as to take common ownership of the entire report.

1.5 WHAT IS THE STRUCTURE OF THE REPORT?

The report comprises seven chapters. Chapter 2 describes the Methodology used in the review. Chapter 3 describes the role of science in the GMO regulatory system. Chapter 4 considers the reliability of GM plant breeding compared with conventional methods. Chapter 5 looks at food and animal feed issues related to safety. Chapter 6 looks at environmental impact and Chapter 7 at gene flow, detection and impact. Chapters 5-7 contain a selection of papers that address

[15] A report on the Corr Willbourn Foundation Workshops can be found on the GM Science Review website.
[16] Chief Scientific Adviser to the UK Government. The letter of invitation from Professor Sir David King to members of the Science Review Panel can be found on the website. http://www.gmsciencedebate.org.uk
[17] Chief Scientific Advisor to the Secretary of State for the Environment, Food and Rural Affairs.

specific issues under each of these headings. A list of abbreviations can be found at the back of the report. Additional Annexes to the Report can be found on the Science Review website[18].

1.6 WHAT IS THE RELATIONSHIP BETWEEN THIS REVIEW AND THE WORK OF STATUTORY UK ADVISORY COMMITTEES ON GM?

In the UK there are extensive regulations that apply to the safety and use of GM crops and their products. Detailed considerations of proposals to release GM crops into the environment or to use them for human food or animal feed are the responsibility of appropriate statutory Advisory Committees. These Advisory Committees consider each proposal on a case-by-case basis and make recommendations to the UK Government. It is then the responsibility of Government Ministers to decide whether or not to implement that recommendation. Regulations covering the cultivation and use of GM crops and their products are complex and are harmonised across the European Union (EU) in the form of EU Directives. These Directives require a detailed science-based risk assessment, and the regulations embodied in them are continually evolving to respond to new knowledge. Further information on the statutory regulatory framework covering the UK is relevant to this Report and is outlined in Chapter 3.

The guiding principle of this Science Review has been to consider the current state of scientific knowledge on specific issues. It is for the statutory bodies to make recommendations based on assessments of specific GMOs[19]. However, this has not precluded a consideration of evidence in particular cases, nor has our brief precluded the identification of new evidence that might bear on these considerations.

1.7 HOW WILL THE REPORT BE USED?

The report is presented to Government as a contribution to future policy and regulatory decisions about GM crops and food in the United Kingdom. The Report from the Prime Minister's Strategy Unit on the overall costs and benefits associated with growing GM crops in the UK was published on 11 July 2003 and the Public Debate strand ('GM Nation?') is due to publish a report in September 2003. The Science Review Panel will then meet again in Autumn 2003 to consider responses to the Science Review report and scientific issues raised by the Public Debate report, and, if timing allows, the results of the Farm Scale Evaluations. The Science Review Panel will produce a second report following these discussions in late Autumn 2003.

[18] http://www.gmsciencedebate.org.uk/panel/default.htm

[19] The terms of reference of the Science Review state that: 'It is not the role of the Panel to make recommendations on specific applications for consent to release or market GMOs. This is the statutory duty of the Advisory Committee on Releases to the Environment (ACRE) and the Advisory Committee for Novel Foods and Processes (ACNFP)'.

Box 1.1: The current status of GM crops and foods internationally

GM crops

The first GM plants (Petunia and tobacco) were produced in 1983 and the first GM field trials in the world were in 1986 and in the UK in 1987. Since that time there has been a rapid increase (% to % p.a.) in the area of GM crops grown internationally, although they still remain a small proportion of the total world agricultural production. Even so, GM crops are now an integral part of agriculture in some countries. Worldwide, commercial cultivation of GM crops increased from 1.7 million hectares in 1996 to 58.7 million hectares in 2002, with soyabean, cotton, maize and rapeseed occupying 99.9% of the area sown. Over a quarter (27%) of the global GM crop area in 2002 was grown in nine developing countries. Globally the principal GM crops in 2001 were soyabean (32% of the global area), maize (21%), cotton (12%) and oilseed rape (5%). The number of farmers growing GM crops was between 5.5-6 million worldwide. More than 75% were small cotton farmers mainly in China and in South Africa.

(Data from - ISAAA Briefs (2002) Preview. Global Status of Commercialized Transgenic Crops: No. 27)

GM enzymes for food production

A range of enzymes for food processing are produced by GM microbes. Chymosin, used mainly for the production of 'vegetarian cheese', is the best-known example. But other examples of enzymic preparations derived from genetically modified organisms which are commercially available for food use in the EU are listed below:

Activity	**Source**
alpha-Acetolactate decarboxylase	*Bacillus subtilis* containing *Bacillus brevis* gene
alpha-Amylase	*Bacillus subtilis* containing *Bacillus stearothermophilus* gene
alpha-Amylase	*Bacillus subtilis* containing *Bacillus megaterium* gene
alpha-Amylase	*Bacillus licheniformis* (self-cloned)
alpha-Amylase	*Bacillus licheniformis* containing *Bacillus stearothermophilus* gene
Catalase	*Aspergillus niger* containing *Aspergillus* gene
Chymosin A	*Escherichia coli K-12* containing calf gene
Chymosin B	*Aspergillus awamori* containing calf gene
Chymosin B	*Kluyveromyces lactis* containing calf gene
Cyclodextrin-glucosyl transferase	*Bacillus licheniformis* containing *Thermoanaerobacter* gene
beta-Glucanase	*Bacillus subtilis* (*B. amyloliquefaciens*) containing *Bacillus* gene
beta-Glucanase	*Trichoderma reesei* containing *Trichoderma* gene
Glucose isomerase	*Streptomyces lividens* containing *Actinoplanes* gene
Glucose isomerase	*Streptomyces rubiginosus* containing *Streptomyces* gene
Glucose oxidase	*A. niger* containing *Aspergillus* gene
Hemicellulase (xylanase)	*Bacillus subtilis* containing *Bacillus* gene
Lipase, triacylglycerol	*A.oryzae* containing *Rhizomucor* gene
Lipase, triacylglycerol	*A.oryzae* containing Thermomyces gene
Maltogenic amylase	*Bacillus subtilis* containing *Bacillus stearothermophilus* gene
Pectinesterase	*Aspergillus oryzae* containing *Aspergillus aculeatus* gene
Protease	*A. oryzae* containing *Rhizomucor* gene
Protease	*Bacillus amyloliquefaciens* containing *Bacillus gene*
Protease	*Bacillus licheniformis* containing *Bacillus* gene
Pullulanase	*Bacillus licheniformis* containing *Bacillus* gene
Pullulanase	*Kleibsiella planticola* containing *Kleibsiella* gene
Xylanase (hemicellulase)	*A. oryzae* containing *Aspergillus gene*
Xylanase (hemicellulase)	*A. oryzae* containing *Thermomyces* gene
Xylanase (hemicellulase)	*A. niger* var.*awamori* containing *Aspergillus* gene
Xylanase (hemicellulase)	*A. niger* containing *Aspergillus* gene
Xylanase (hemicellulase)	*Bacillus subtilis* containing *Bacillus* gene
Xylanase (hemicellulase)	*Bacillus licheniformis* containing *Bacillus* gene
Xylanase (hemicellulase)	*Trichoderma reesei* containing *Trichoderma* gene

Chapter 2

METHODOLOGY

This Review is conventional in that it evaluates the current state of scientific knowledge in the field. In other respects, it is distinctive. Scientific reviews are often 'in house affairs' aimed at a specialist scientific community. But, in addition to having scientific integrity, this Review has been designed to be conspicuous, and to be explicitly linked to public interests and concerns.

In the first phase of the Review, all scientists and the general public were invited to submit papers and science-based views on key issues. Letters of invitation were sent to large numbers of individuals to encourage the widest participation from scientists of all shades of opinion.

The second (peer review) phase enabled the Science Review Panel to consider the scientific rigour of the papers presented (and other information available) before summarising where consensus lay on the science and where there is real uncertainty or gaps in knowledge.

Figure 2.1 shows the routes of information exchange between the various components of the GM Review that are described in detail below. The Timetable of the Review is shown in Table 2.1.

2.1 PUBLICITY

The launch of the Science Review was publicised in the media to stimulate interest among the scientific community and more broadly. As well as tapping into familiar expertise, it also wanted to reach out widely to access fresh sources of knowledge that might offer new perspectives on GM issues. The communication strategy included a letter to the scientific community and high profile media interviews.

2.2 THE WEBSITE

Launched on 31 November 2002, the Science Review website provided the principal means by which the scientific community and the general public could contribute to and observe the Science Review. It also provided the principal medium by which the Panel communicated on the science and looked at the evidence. Neither the Web nor science has geographical boundaries. Although the Review was focused on UK issues, it invited contributions on an international scale. The website provided details of Panel meetings (Agendas, Secretariat papers, Minutes, instructions for members of the public who wished to observe), and Open Meetings (registration details, speakers abstracts, verbatim transcripts, reports specially commissioned by science writers).

Guidance on how to make contributions was also provided on the website. Although contributions did not need to be peer-reviewed, contributors were encouraged to focus on and address the science, which should be reasonably argued and be evidence-based, either directly

or by reference to identified and publicly available material. A gratifying feature of the Review was that most contributions conformed to these guidelines. Those that did not were not excluded but placed on a 'wider issues' page of the website. At the time of writing almost one hundred contributions have been received. The names and status of the scientists submitting contributions was requested so that readers could judge for themselves the accountability and experience of each contributor.

An 'interests and concerns' page was developed to make the Review especially accessible to the public. This hosted a review of public concerns (the Corr Wilbourn Report), questions arising from a series of foundation discussion workshops, popular summaries of Science Review Open meetings held around the UK written by science writers, and a glossary of terms.

2.3 THE SCIENCE REVIEW PANEL

The Science Review Panel, chaired by the Government Chief Scientific Advisor, Professor Sir David King, working with Professor Howard Dalton, Chief Scientific Advisor to the Secretary of State for Environment, Food and Rural Affairs, had two principal functions. First, to monitor the progress, quality and credibility of the Science Review itself and second, towards the end of the debate, to review and summarise the state of scientific knowledge, consensus and identify significant/relevant areas of uncertainty.

Two distinguishing features marked out this Panel immediately. Firstly it was quite large (25 members) and secondly, it has an exceptional breadth of expertise and experience including leading scientists and social scientists from a number of fields, and with a spectrum of opinions on GM. There was overlapping membership between the Science Review Panel and the Steering Group of the GM Public Debate, to help ensure that the scope of the Science Review evolved in the light of developments in the public debate. Details of Members and their affiliations and expertise and interests can be found on the website.
(http://www.gmsciencedebate.org.uk/panel/members/default.htm)

The Science Review Panel met on seven occasions over a six-month period, mostly at the Royal Society or the Royal Institution of Great Britain. Members of the public were able and encouraged to observe these meetings. Minutes can be viewed on the website.

Early in its work the Panel identified areas of interest and concern to the scientific community. It also took into account public attitudes through consideration of the outcome of the foundation discussion workshops published in the Corr Willborn Report, and developed a framework to review these issues. The Panel looked at contributions to the website, the Open Meetings, as well as reviewing the scientific literature. At several meetings members discussed at length, particular topics of concern raised by members of public that were posted on the Science Review website. These are recorded in the minutes and secretariat papers which can be found on the website.

2.4 OPEN MEETINGS

Between January and March 2003, a programme of four open meetings was organised by the British Association for the Advancement of Science (BA). The purpose of these meetings was to offer a wide spectrum of scientists the opportunity to put their views to the Science Review Panel and for the public to have an opportunity to enter into dialogue with experts. Diverse venues were chosen: The Science Museum (London), The Royal Society of Edinburgh, The Institute of Grassland and Environmental Research (Aberystwyth) and the Agriculture and Food Science Centre (Belfast). They were all well attended, with audience numbers ranging from 70 to 100. A fifth Open meeting was organised by the Royal Society itself in London.

Further details including programmes, reports and verbatim transcripts can be found on the Open Meetings page on the website.

2.5 STRAND CO-ORDINATION

Following the initial announcement of the GM Review by Rt. Hon Margaret Beckett MP, the three strands have developed their strategies and operations in close consultation with each other, recognising that good interaction is essential for success. The Science Review recognises that the GM debate is a very deliberative means of engagement with the public. The GM Science Review Panel was constituted with a deliberate element of cross-skills membership. Professor Philip Dale served on the Public Debate Steering Board and the Science Review Panel. There has been comprehensive two-way flow of information with the Strategy Unit, especially in those areas where there are direct linkages between their work and the Review. For example, the Strategy Unit held a shocks and surprises workshop to look at various scenarios and the review paper on allergenicity (Section 5.3) explicitly took into consideration a very specific scenario discussed at this workshop. Two members of the Science Panel also have roles on the Strategy Unit expert groups (Professor Jules Pretty and Dr Brian Johnson) and others have contributed to seminars held by the Strategy Unit as part of their work. The work published by Corr Willbourn on the outcome of the public debate foundation discussion workshops to assess grass roots interests and concerns has played a central role in setting the agenda of the Science Review process.

2.6 THE FRAMEWORK OF THE REVIEW

2.6.1 Framework

The Panel developed the framework in Box 2.1 to review the issues. The Framework is broader in extent than the checklist (Box 2.2) and specifically governs the structure of our sections in our Review; whereas the checklist was a discipline the Panel agreed it would go thought to respond to the questions raised in the framework. For each issue the Panel consider the following:

Box 2.1: Review Framework

1 **Range of views and quality of evidence.** What is the range of views based on peer-reviewed literature and other sources of information, and what is the quality of the evidence? Have all major perspectives been brought to the Panel? (See Checklist, point 1.)

2 **Is there general scientific agreement?** (See Checklist, point 2.)

3 **Is the issue unique to GM?**

4 **Are there gaps in our knowledge or scientific uncertainties and are these important?** What is or what might be the risk associated with the uncertainty? (See Checklist, point 4.)

5 **Looking to the future.** What potential developments are there is this area? Do they affect the Panel's conclusions?

6 **Where there is recognised scientific uncertainty, what is the potential way forward?** (See Checklist, points 5 & 6.) For example:

- Further research?
- Are there technological approaches or agronomic practices that could help to reduce uncertainty?
- Are there satisfactory regulatory approaches, e.g. assumptions in risk assessment, monitoring, tools to evaluate the risks?

It is important to recognise that closing gaps in knowledge may not always be possible in practice for all sorts of reasons, including technological or economic constraints.

2.6.2 Checklist

The overall aim of this Checklist was to provide a single consistent framework to assist the Science Panel to respond in an efficient and coherent fashion to issues identified from a variety of sources. These include questions formulated by the Panel itself, those arising from Open Meetings and the Public Debate, and those raised in submissions to the Science Review website.

The Checklist attempted to fulfill a number of objectives. It embodied the remit of the Science Panel to give (and be seen to give) full attention to 'uncertainties', 'divergences of view', 'unknowns', and 'gaps in knowledge'. It aimed to be clear and meaningful for a general audience, whilst helping to stimulate relevant and fruitful questions of specific bodies of scientific evidence. It assisted the Panel in addressing the full scope of public concerns over GM science whilst avoiding repetitive, time-consuming or unduly onerous burdens.

The Checklist comprises six basic questions. These are divided into two groups, concerning, respectively, 'what do we know' and 'what don't we know'. Each question is supported by a short explanatory paragraph.

Box 2.2: Review Checklist

What do we know? How robust is this knowledge?
1 What is the quality of the evidence? Where there are judgements over the relative likelihood of different outcomes, is this based on empirical field data, laboratory studies, scientific models or expert opinion? In considering different hypotheses, have false negatives been treated the same as false positives? What is the statistical power of any quantitative assessments? **2 Are there different interpretations of the evidence?** Does the Panel's response include attention to contending scientific understandings or minority expert opinions, both within the Panel itself and in the wider literature? What are the implications of any such divergent interpretations for the conclusions reached by the Panel? **3 What key assumptions do the Panel's conclusions rely on?** Which assumptions, if altered, might have a significant effect on the Panel's conclusions? For instance, what assumptions are adopted with respect to operating environments, individual behaviour, adherence to good practice, regulatory compliance or institutional trends? What would be the effect of altering these key assumptions?
What don't we know? How might we cope with this?
4 Might there be significant gaps in our knowledge? Are there scientifically founded questions concerning the completeness, sufficiency or applicability of the scientific models or data which inform the conclusions reached by the Panel? What can be said about any resulting 'unknowns' and their practical implications? **5 How might research help to address the gaps?** What kinds of scientific research or environmental (or other) monitoring might help to reduce particular uncertainties or address the unknowns identified by the Panel? **6 What risk management measures might help to address these gaps?** What operational practices or policy measures might help to address the key scientific uncertainties and unknowns identified by the Panel or to mitigate exposure to their consequences? What might be the limitations of these measures?

2.7 THE REVIEW OF PUBLIC CONCERNS (THE CORR WILLBOURN REPORT)

The work published by Corr Willbourn on the outcome of the public debate foundation discussion workshops to assess grass roots interests and concerns has played a central role in setting the agenda of the Science Review process. This work was an integral part of the GM public debate strand of the National dialogue. A copy of the report can be viewed on the Science Review website. The introduction to each Review chapter lists the 'questions' of particular relevance to science under Review. The questions are listed at Annex I.

Figure 2.1: Information exchange

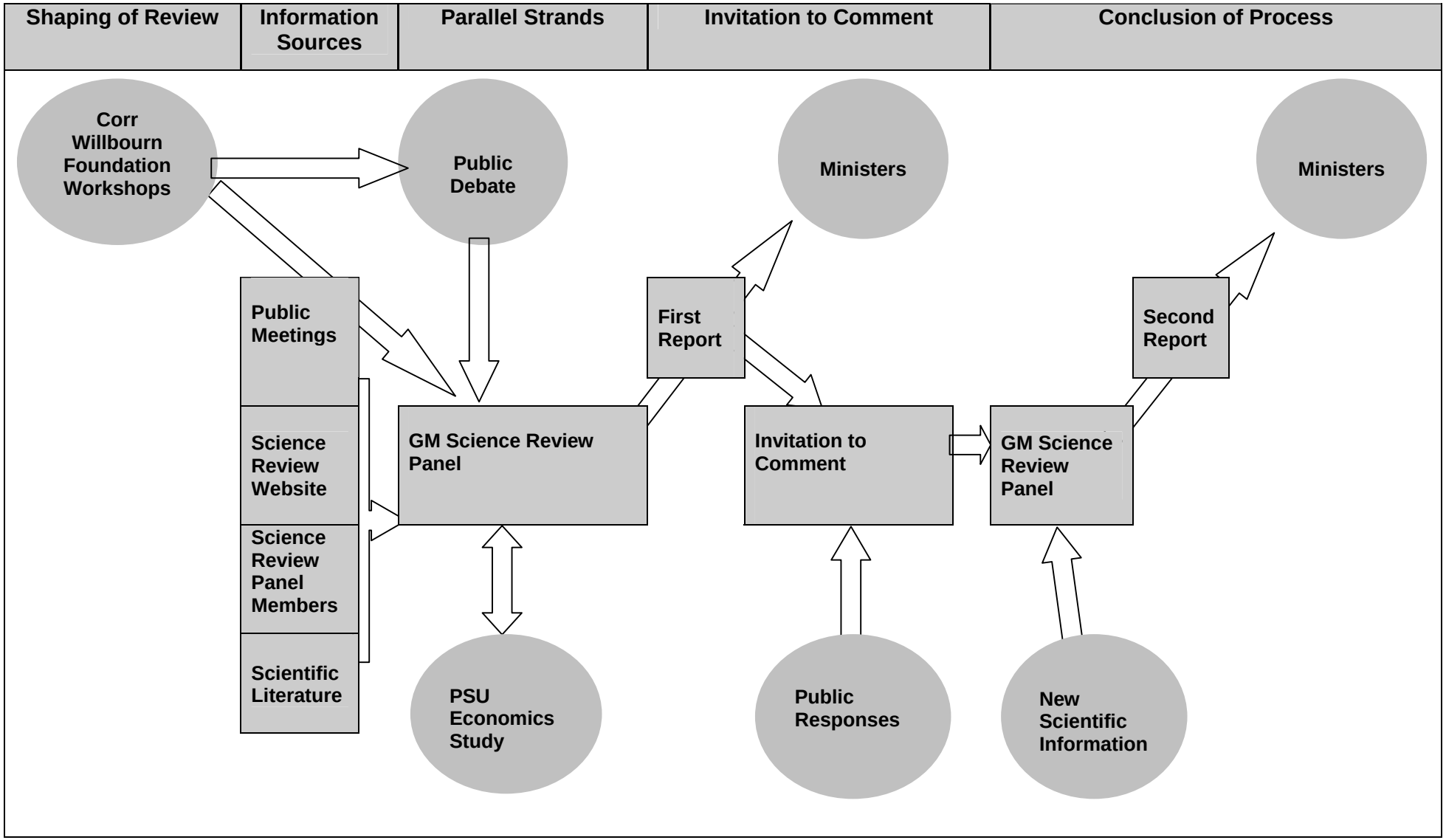

Table 2.1: Timetable

2002/2003	November	December	January	February	March	April	May	June	July
Dedicated Website	Launch								
Science Review Open meetings			23rd Science Museum, London 27th Royal Society, Edinburgh		11th Agriculture & Food Science Centre, Belfast 17th Institute of Grassland & Environmental Research				
Science Review Panel Meeting		10th		18th	19th	29th	13th	5th, 24th	
Drafting Group Meetings						1st Food & Feed Group 2nd Environmental Impacts Group 8th Geneflow Group	13th All three Groups		
Corr Wilborn report published					6th				
Public Debate Programme								3rd start	18th finish
Strategy Unit									Report
Science Review									First Report to Ministers

Chapter 3

SCIENCE IN THE REGULATORY PROCESS

This chapter describes the role of science in the regulatory process. Science has a central role in the regulation of genetically modified organisms because it provides the evidence base for decisions on safety to human health and the environment, and it is on the basis of safety (not benefits), that approvals are granted.

The regulatory process is dynamic, continuous (in that no approval is absolute, it is always under review to take account of advances in science and technology and prevailing knowledge), subject to critical challenge and continuously subject to improvement. It is through critical challenge that, for example, the farm scale evaluations and subsequent changes to European regulatory framework have taken place. The regulatory system will improve in future because we will improve understanding of the limitations of the scientific basis of the regulatory process and develop new tools to refine risk assessments.

Applications to cultivate GM crops, or to place foods or animal feed derived from them onto the market, are reviewed by scientists serving on advisory committees. In the UK these are: the Advisory Committee on Releases to the Environment (ACRE); the Advisory Committee on Novel Foods and Processes (ACNFP) and the Advisory Committee on Animal Feeding stuffs. Each has websites where detailed information is available.

The scientific quality of the initial scientific evidence submitted to these committees by applicants varies, and a process of iteration often follows between the committee and applicant with the applicant providing further information before the committee can formulate its advice (see Figure I) which gives an overview of how ACRE operate; other committees follow similar procedures). The application dossiers and the committees' advice are publicly available. Some of the evidence in dossiers is based on peer reviewed published papers. However, other material is based on 'in house' research and unpublished. The reasons for not publishing work are varied but it does not necessarily follow that the work is substandard. Science advisory committees in evaluating dossiers essentially 'peer review' unpublished data in the course of their evaluation.

Genetically modified organisms are required by legislation to be assessed on an individual, case-by-case basis. Consents are issued for a limited duration (for both field research or marketing applications) under specified conditions that might also include monitoring requirements. Consents can be withdrawn if regulatory examination of subsequent evidence finds the product unsafe or insufficiently safe.

Scientific advisory committees operate within the bounds of what is widely regarded as acceptable scientific standards of conduct and process (see background of Introduction for a more detailed explanation of what this means). Conditions are attached to consent and the consent holder is expected to adhere to good practice and regulatory compliance. The GM Inspectorate's role is to check for compliance.

Science is continuous and developing and there are often divergent viewpoints across the science community on issues. It is not necessarily the data which is disputed, but it can be its interpretation. Committees advise on the basis of current and widely accepted state of scientific knowledge and advice is reviewed in the light of latest scientific developments. Committees are not insulated from the scientific community or public concerns. The most recent large-scale example of public engagement in the UK has been the Chardon LL GM maize hearing.

As approval is based on safety to human health and the environment, a risk assessment carried out by the applicant forms the core of the applications. The scientific advisory committee assesses this. The risk assessment does not consider economic costs and benefits.

It is important to recognise the difference between hazard and risk. Confusion between the two can and does lead to problems in risk communication. A hazard is something that may cause harm. Risk is the product of two components: the likelihood that the hazard will take place and (in the event that it does) the consequence.

The relationship between hazard and risk is often illustrated by the function:

Risk = f (hazard, exposure)

Some generic limitations have been noted in the conventional risk assessment of complex technologies (Arrow, 1971; Porter, 1995; Wynne, 1996; Power, 1997; Morgan et al, 1990; Shrader-Frechette, 1990; Wynne, 1992; Amendola *et al.* 1992). The existence of these limits is a prominent theme in much of the international policy literature on risk assessment (DoE 1995; NRC, 1996; Treasury (UK), 1996; EPA, 1997; RCEP, 1998; HSE, 1999; House of Lords, 2000).

Scientific advisory committees operate in this complex climate and are aware of the challenges in providing advice. Committees such as ACRE have for example, grappled with some of the difficult issues related to what is environmental harm; provided guidance to raise the standards of submissions; and developed principles of best practice in the design phase of making GM crops; provided guidance on monitoring[1]. The philosophy of best practice in GM crop design is essentially an avoidance strategy to reduce unidentified risks. The approach minimises opportunities for potential harmful interactions to occur that may be difficult to anticipate, to evaluate or to monitor.

Science advisory committees, in assessing applications on a case-by-case basis, make use of a number of practical approaches to managing risks. Removing or 'bagging' flowers where there is uncertainty about the impact of cross-pollination is an example. Or, if there is no qualitative data on an event occurring, simply assuming it does occur and then estimating the consequences. This is particularly relevant in assessments on gene transfer to plants that can exchange genes in the field, or horizontal gene transfer where there is uncertainty about whether it occurs.

[1] http://www.defra.gov.uk/environment/acre/subgroups.htm

Chapter 6, Section 6.8 is relevant to those interested in considering further the main scientific approaches available for determining and predicting the environmental consequences of GM crops.

3.1 SUBSTANTIAL EQUIVALENCE

For many years now, the concept of 'substantial equivalence' has been a prominent feature of established international approaches to the regulation of GM technologies (CEC, 2003). It is not a safety assessment in itself but a way of structuring the comparison of a novel food with its conventional counterpart to identify any differences that then become the focus of the safety assessment. It recognises the fact that for most conventional foods, acceptable safety is established by their history of consumption rather than by formal risk assessment.

Substantial equivalence is used to identify differences that potentially could compromise this established level of safety in a conventional food. The approach is needed since standard animal toxicity tests designed to evaluate single defined chemical substances like food additives, pesticides and pharmaceuticals cannot be done on whole foods without careful consideration of nutritional implications. It is difficult to feed an animal a sufficient multiple of the anticipated human intake of the food being tested without compromising the nutritional balance of the test animal. The Food and Agriculture Organisation of the United Nations (FAO) and the World Health Organisation (WHO) first addressed this problem in 1990 when the principle of comparing a new food with an existing food was identified. In 1991 the OECD formulated the concept of substantial equivalence. It has been revisited frequently since its inception and was reviewed in 2000 by FAO/WHO who found it to be a practical way to structure the safety assessment of foods.

In the past, substantial equivalence has been applied to determine an 'end point' in the safety assessment process (OECD, 1993). In this context it provides evidence that a GM crop or product is 'substantially equivalent' to a non-GM counterpart. The legislation on GM food and feed (see Appendix 2) has included this provision but it is little used and will not feature in new GM regulations that are about to be introduced. This application of substantial equivalence has been subject to significant criticism (e.g. Millstone *et al*. 1999; Royal Society of Canada, 2001; Levidow and Murphy, 2003).

Currently, substantial equivalence not used to determine a regulatory 'end point' but rather it is the framework for a comparative approach (SBC, 2001) that guides safety assessment. Significant differences between a new food and its traditional counterpart are identified as a basis for further investigation. The comparison identifies similarities and differences between the novel food and the existing counterpart with respect to composition, nutritional value and metabolism. The safety assessment then focuses on the health implications of any identified differences, which may or may not represent a hazard. For GM foods, the safety evaluation considers in detail:

- the genetic modification event including history of the host organism as well as the characterisation of the modified organism;
- safety assessment of the new gene product(s) and or metabolites;
- composition (fats, proteins, carbohydrates, vitamins, minerals) of the food;

- potential toxicity;
- potential allergenicity;
- any unintended secondary effects; and
- likely intakes and dietary impact.

Importantly, the end result is a decision on food safety and not a conclusion based solely on an analysis of similarity.

Readers who are particularly interested in food and feed safety may wish to refer to Chapter 5.

3.2 THE PRECAUTIONARY PRINCIPLE

The second key general concept bearing on the regulation of GM crops is 'precaution' (Cameron and O'Riordan, 1994; Sand, 2000; Fisher and Harding, 1999; Raffensberger and Tickner 1999; O'Riordan and Jordan, 2001). This is formally enunciated in various versions of the 'precautionary principle', which holds, in one influential version, that '*…Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.*' (UNCED, 1992). Although providing a general evaluative guide, precaution has (like substantial equivalence) also been criticised on the grounds of scientific ambiguity (USDA, 2000; ILGRA, 2001). How serious is 'serious'? What exactly do we mean by 'irreversible'? How should we define 'full scientific certainty'? Concerns are raised that precaution constitutes an essentially pessimistic response to uncertainty and gaps in knowledge in regulatory risk assessment (Morris, 2000).

However, over recent years precaution too has begun to be interpreted in a somewhat different and more concrete fashion (ESTO, 1999; EEA, 2001). Rather than being treated as a firm 'decision rule', precaution is increasingly seen in terms of what it means for the regulatory appraisal process (Stirling, 2003). In this respect, precaution appears as an inherently scientific response to challenges of uncertainty, ambiguity and gaps in knowledge: by providing practical guidance to the types of information that might best inform decision-making and the most effective ways to gather this information (Renn 2003; van Zwanenberg and Stirling, 2003).

In particular, a precautionary approach to the appraisal of risk is generally held to embody the series of specific elements summarised in Box 3.1 (after ESTO, 1999; EEA, 2001). To the extent that the present Science Review process embodies many of these general characteristics, then it may be seen as part of a genuinely precautionary approach to the appraisal of GM food and crops.

Box 3.1: A summary of key characteristics of a precautionary approach to the appraisal of risk (after: ESTO, 1999; EEA, 2001; Renn, 2003)

- The inclusion of diverse scientific disciplines, to guard against an unduly narrow idea of the possible hazards, conditions or mechanisms of harm.
- The careful treatment of evidence, so that absence of evidence of harm is not presented as evidence of absence of harm. This is associated with a certain shift in the levels and burdens of proof, such as to give greater favour to the environment and human health.
- The open acknowledgement of uncertainty, ambiguity and gaps in knowledge, in order to avoid concealing the role of subjective judgement and the intrinsic limitations of risk assessment
- The transparent documentation of any assumptions and value judgements and an exploration of their scientific consequences by means of techniques like sensitivity and scenario analysis
- The involvement of stakeholders, lay people and participatory techniques to help ensure that the 'framing assumptions' explored in scientific analysis are consistent with wider social interests and values.
- The systematic and balanced assessment of the pros and cons associated with a series of different options, rather than simply focusing on the 'acceptability' of a single option in isolation or a comparison between this and existing tolerated poor or worst practice.
- Ensuring that the appraisal process allows expression of a balanced array of opinions, free from the exercise of coercive pressures and as independent as possible from particular financial or political vested interests.
- The serious consideration of issues such as the irreversibility of possible harm, the flexibility of possible responses, the diversity of policy options and the ease with which associated commitments may be withdrawn, to ensure that strategies are as robust as possible in the face of new knowledge and surprise.

Chapter 4

HOW RELIABLE IS GM PLANT BREEDING?

Does GM work? Is GM technology too imprecise? Are GM genes more unstable than resident genes? Is it necessary to produce many transgenic plants to obtain an acceptable one?

4.1 Summary

Some people have expressed concern that GM plant breeding is too unreliable and imprecise for crops to be used in agriculture at all or at least without more extensive testing. A principal argument used is that it is necessary to produce about 100 GM plants to obtain one that has desirable characters for use as a basis of a new GM crop variety. To address this concern it is necessary to place GM breeding in the context of non-GM breeding methods such as: gene transfer by pollination, mutation breeding, cell selection and induced polyploidy. Most of these now conventional plant breeding methods have a substantially greater discard rate. Mutation breeding for instance, involves the induction of unpredictable large-scale and undirected genetic changes. Many thousands (or millions) of undesirable plants are discarded in order to identify plants with suitable qualities for further breeding. Mutation arising spontaneously is the ultimate source of all variation allowing plant breeding and evolution.

The current and widely accepted view within the biological research and plant breeding community is that there are important parallels between non-GM and GM plant breeding although in certain respects GM breeding techniques differ significantly, and that the methods of evaluation of GM crops for food, feed and the environment currently carried out within the European regulatory framework, are generally robust if consistently applied and should be effective. All plant breeding methods have unique features. The special feature of GM plant breeding is that it allows a wider choice of genes for modifying crops in novel ways by enabling the use of genes from species outside the plant kingdom (animals, bacteria and viruses). This undoubtedly presents challenges for their regulation and management so that (along with non-GM crops) they will need to be addressed carefully and intelligently as GM breeding techniques evolve.

It is important that in the UK we have regulatory oversight that is proportional to the degree of risk, which recognises the distinctive attributes of GM and the different sources of uncertainty as well as the conventional breeding context and baselines.

4.2 Background

Modern molecular biology methods make it possible to isolate genes, and other DNA sequences, from different organisms or make synthetic DNA, and insert the DNA into crop plants. Usually many individual GM plants need to be produced to obtain a crop variety that has desirable qualities for use in agriculture and for consumption. This has led to expressions of concerns that GM technology may not be sufficiently precise and reliable. As this issue is relevant to food, feed and environmental impact, it is being considered in a separate chapter in this report. To address the topic, it is first important to discuss GM plant breeding in comparison with other methods of plant breeding (see Hayward *et.al.* 1993; Smartt and Simmonds, 1995; IAEA, 1995[1])

4.2.1 How different are GM and non-GM plant breeding methods?

Non-GM plant breeding includes a wide range of approaches. Some non-GM methods have been used throughout the history of plant breeding, and others apply the latest advances in molecular genetics and genetic mapping. Some examples are as follows.

Gene transfer by pollination involves the transfer of genes into crops by pollination with plants usually from the same species, but occasionally from different species or different genera. This is the basis of cross-breeding. This method makes it possible to recombine many thousands of genes from different plant parents. Plant embryo culture has extended the range of cross-breeding and made it possible to obtain hybrid plants that are unlikely to form in nature. Plants with desirable genetic combinations are selected and undesirable ones discarded following extensive testing of (tens of) thousands of genetically different plants.

Induced mutation in its simplest form involves exposing seeds or seedlings to ionising radiation (Cobalt60 gamma) or chemicals (mutagens) that cause unpredictable random changes (mutations) in the genes of the final crop plants. Some mutagens cause predominantly random single DNA base-pair substitutions, others cause random breaks in chromosomes, loss of chromosome fragments or rejoining of chromosomes in different combinations. A more subtle form of induced mutation is to induce destabilisation of naturally occurring mobile genes (transposons) that have the potential to silence other genes or cause them to be expressed in novel and unpredictable ways. The utility of mutation breeding relies on careful evaluation and selection of plants with desirable qualities in the progenies of the first generation mutants. This frequently involves the elimination of (tens of) thousands of plants with undesirable characters. Mutation breeding underpins the plant breeding pedigrees of many of the food crops we eat daily (especially cereals)[2].

Cell selection requires crop plants to be grown in culture vessels in a laboratory. The DNA in cell cultures becomes genetically unstable and this instability is used as a source of genetic variation for plant breeding. This method has been used, for example, in the selection of

[1] These three publications, and the references they cite, provide comprehensive reviews of plant breeding methods and the evolution and breeding of a range of crops.

[2] http://www-mvd.iaea.org/MVD/default.htm is reference to the list.

herbicide tolerance in crop plants (Marshall, *et al.* 1992). Herbicide is simply added to the culture media and plant cells that survive are rescued and used to regenerate whole plants with increased tolerance to the chemical. The method inevitably incorporates other mutations with unknown effect as part of the cell selection process. As with tissue culture methods there is evidence of random genetic changes in cultured cells (Karp, 1991) and the destabilisation of naturally occurring mobile genes. Where these extra mutations deleteriously affect the agronomic performance of the plant, they can, in some crops, be removed by undertaking conventional backcross programme to incorporate the trait in an otherwise acceptable genetic background.

Induced polyploidy involves treating plants with a chemical (such as colchicine); that doubles the number of chromosomes[3] in the crop and, therefore, doubles the amount of DNA in every cell in the crop plant. Induced polyploidy has been used in the breeding of some of the grasses, clovers and horticultural crops used commercially. It is also used in the breeding of other crops, especially for the production of interspecific and intergeneric hybrid crops e.g. hybrids between wheat and rye (triticale).

Molecular marker assisted breeding. A substantial and growing body of genetic information on crops is now making it possible for plant breeders to recombine and select genes where previously this has been impossible on a rational basis. Plant characters controlled by several genes, and those difficult to assess phenotypically (such as yield, or resistance to drought and salt) have traditionally been very difficult to modify by breeding. The use of molecular markers is significantly improving this efficiency and has the potential to allow breeders to assemble new groups of genes such as multiple disease resistance genes, to effect novel changes in crop plants.

Targeting induced local lesions in genomes (TILLING). Advances in genetic sequencing of crop plants mean that it is now possible to effectively select induced mutations in specific plant genes (Colbert et al, 2001). This advance in research and methodology is beginning to provide unique opportunities to modify the biosynthetic processes of plants in ways previously inaccessible to plant breeders. In the coming decade, with further advances in genetic mapping and gene sequencing, it is likely that plant breeders will be able to modify a range of crop characters in novel ways.

GM plant breeding. By comparison with the 'non-GM' plant breeding methods (described above), GM allows the incorporation into crops one or more specific gene sequences isolated from a range of classes of organisms. These can be: the same crop species, wild relatives of the crop species, other quite different plant species, microbes (viruses, fungi or bacteria) or even animals. The method can be used to incorporate one or several genes into a crop plant that has many thousands of genes (wheat probably has more than 100 thousand genes). As the inserted gene will have been characterised at the molecular level (its genetic information defined), its position in the genome and its function can be assessed with a greater degree of precision than for genetic changes made by most non-GM plant breeding methods. It is necessary to produce about 100 GM plants to obtain one that has the desired qualities following testing and evaluation. The remainder are discarded.

[3] A chromosome is a thread like structure in the cell nuclei that carries genes. Wheat has 42 chromosomes, barley has14 chromosomes and potato has 48 chromosomes.

All of the above methods have unique properties and find utility in specific breeding applications. GM breeding cannot be used to make polyploids, or recombine thousands of genes (pollination), or cause large-scale random unpredictable genetic changes (mutation breeding). Similarly mutation breeding cannot be used to introduce single genes into crops from radically different organisms (GM breeding).

4.3 Range of views and quality of evidence

This section considers some general concerns that have been expressed about GM technology and whether it is sufficiently developed to produce crops that are safe for food, feed and the environment in comparison with non-GM crops. The question in the Foundation Workshop report[4] of most relevance is: 'does GM work?'

Within the Science Review process, these questions were discussed mainly at the second meeting of the GM Science Review Panel and at the Open Meetings on 'GM Food Safety'[5]. Issues raised in contributions to the Review website included: comparisons with radiation induced mutagenesis; unpredictability, imprecision and scientific uncertainty in GM; the instability of transgenic DNA; and the high rejection rate of plants resulting from the GM process.

4.3.1 Range of views

It is necessary to produce about 100 GM plants to produce one that has a desirable combination of crop characters. Some view this as demonstrating that GM technology is too imprecise. Others consider that GM plant breeding is considerably more precise than many non-GM methods, and that the tests required in the assessment and regulatory process are sufficient to identify desirable GM plants and GM crop varieties.

Introduced transgenes are observed to vary in their effect on the plant and to be influenced by environmental conditions. Some view this as demonstrating that GM genes can be unstable and may behave differently from resident (endogenous or existing) genes, giving rise to important uncertainties. Others note that genes introduced by non-GM methods can also show variable effects and be influenced by the environment (Griffiths *et al.* 1993). They also consider that the extensive testing of GM plants ensures that the plants used to establish new GM varieties present no greater risk than non-GM crops (most of which have not been through comparative testing). Others are less confident and take the view that it cannot be ruled out for either GM or non-GM plants that such effects may not be manifested until they are in widespread use.

Views about the unintended effects of GM crops vary. Some consider that unintended effects may pose health risks. Others consider that the theoretical planning of the transgene constructs

[4] The Corr Willbourn Foundation Workshops report can be found at http://www.gmnation.org.uk/docs/corrwillbourn.pdf

[5] http://www.gmsciencedebate.org.uk/meetings/default.htm

and procedures, the selection of the transgenic plants, the trials of the new crop variety and finally tests required during the regulatory process are sufficient to detect undesirable properties.

Some reason that the long history of plant breeding means that phenotypic variation typically falls within a familiar range, yet even a single gene inserted via GM techniques can produce a plant phenotype of which there is little or no experience (Dale and Irwin, 1998).

There is variation in views about the nature of evidence required to conclude that GM crops are acceptably safe. Reflecting a basic principle of scientific inference, some argue that the absence of evidence of harm should not be treated as evidence of the absence of harm. This argues for greater reliance on scientific research and epidemiological monitoring. Others reason that the combination of testing by developers to satisfy regulatory requirements for clearance and extensive use around the world over long time periods and large exposed populations and absence of evidence of harm, does provide important experience of safety[6]. Many millions of tonnes of GM crops have been produced and consumed internationally over the past eight years without any substantiated evidence of harm when compared with non-GM crops. However, views vary on what kind of monitoring is necessary and how many years and millions of tonnes of GM crops should be grown and consumed to draw a conclusion of acceptable safety.

4.3.2 Quality of evidence

The number of transgene constructs inserted into the plant genome during genetic transformation usually ranges from one to three, but can be higher. Plant breeders generally select and use transgenic plants with a single inserted transgene construct. This simplifies subsequent transgene inheritance patterns, and any further breeding. Selection of single inserts also simplifies the molecular analysis needed to satisfy the regulatory risk assessment (Lindsey, 1998; Bavage *et al.* 2002).

The positioning of transgene constructs in the plant genome varies between different GM plants. Transgene insertion mutagenesis practised most comprehensively in *Arabidopsis*, but also now extensively in rice (Martienssen and Springer, 1998; Jeon, J-S *et al.* 2000), demonstrates that transgenes can cause insertion mutations in resident genes more or less throughout the plant genome. For risk assessment purposes it is, therefore, assumed that all endogenous genes are potentially exposed to the insertion of transgenes within and adjacent to them during the transformation process. The evaluation and testing required for GM organisms is based on this assumption. It is also assumed that naturally occurring mobile genes (transposons found widely in crops and other living things) in non-GM methods of plant breeding are capable of causing similar disruptions (Griffiths, 1993). The behaviour and consequences of mobile genes have been studied extensively in maize since the 1940s and many mutations from this cause have been described (Brutnell, 2002).

There is variation in the extent of border DNA sequences that are inserted into different transgenic plants during the transformation process (Lindsey 1998). Border DNA sequences are

[6] Very few species giving the foods we eat daily have been tested for safety at all, and certainly not as extensively as GM crops for foods and feeds. We rely principally on our experience of safe use.

those from the plasmid or vector used for the transformation, but lying outside the specific DNA designed for transformation. This is true for transformation by *Agrobacterium* and the gene-gun, but the identity of the border sequences is more predictable for *Agrobacterium* transformation. Regulatory risk assessment requires molecular analysis of the molecular integrity of the inserted transgene construct, including the extent of any DNA outside the immediate transgene construct. If detailed molecular data are not provided in a proposal to the regulatory authorities to carry out an experimental field release (for instance), an assumption should be made that the whole plasmid has been inserted and a risk assessment carried out on that basis.

Tissue culture methods are used in most transformation procedures and these can sometimes be associated with an enhanced rate of mutation or epi-mutation (induction of heritable variation other than through DNA sequence changes). This source of novel variation has been studied extensively in its own right (somaclonal variation) for plant breeding. The mutations can be of various types, including: point mutations, deletions, duplications and chromosomal mutations including loss or gain of whole chromosomes (Karp, 1991). Mutation is a natural phenomenon that occurs in all living things and is the original source of all differences between genes on which sexual genetic recombination and natural selection act during evolution of new species. Mutation frequency can be increased by various methods (chemicals and irradiation) and different forms of induction have been used widely as a plant breeding tool (as discussed). The frequency of mutation and epi-mutation is normally higher than is seen in seed-propagated plants, but much lower than in mutation breeding programmes. The phenotypic and molecular analysis required during selection of plants by plant breeders, and subsequently the regulatory risk assessment, is designed to detect significant changes of this kind. The extent and stringency of analysis of transgenic crops is substantially more exacting than for the products of spontaneous mutation (e.g. 'sports'[7]) or breeding with induced mutations.

There is sometimes variation in transgene expression in the early plant generations and phases of testing. During the first generation of transgenic plants (T0) there can be non-Mendelian inheritance[8] patterns because of the insertion of multiple copies of the transgene and sometimes because of chimeras where some shoots and flowers are transgenic and others not. In subsequent sexual generations, where plants are selected with single copy transgene inserts, genetic segregation patterns usually follow the expected Mendelian ratios. In a plant breeding programme, any plant that has undesirable characteristics (e.g. transgene expression levels are too high, too low or not in the appropriate tissues of the plant) is discarded just as in traditional breeding programmes.

Transgene expression can sometimes be silenced or altered in transgenic plants and in subsequent sexual generations. There is now an extensive literature on transgene silencing which shows that DNA homology between different transgenes, or between transgenes and resident genes, can result in gene silencing (Meyer 1995; Grierson *et al.* 1996; Matzke 2002). Indeed the phenomenon is sometimes used to modify plant phenotype (i.e down-regulate expression of endogenous genes in the original plant), or give resistance to infection by preventing expression of genes causing disease in transgenic varieties. Many aspects of the phenomenon of transgene

[7] 'Sports' are naturally occurring mutations that have been used as a source of genetic variation for plant breeding, especially in vegetatively propagated crops e.g. potato.

[8] Inheritance does not follow Gregor Mendel's laws of single gene inheritance.

silencing have been elucidated over the past decade. It is known for instance that infection of Brassica plants with a caulimovirus can silence transgenes regulated by DNA sequences originally taken from the same virus (Al-kaff, *et al.* 1998). The possible consequences of gene silencing depend on the particular transgenic modification and need to be assessed case-by-case. The silencing of a herbicide tolerance gene, for example, could cause the crop to become susceptible to the herbicide (Al-Kaff, *et al* 2000). A potential application of gene silencing is to remove an allergenic protein from a food crop. Crops with this application of silencing would need to be assessed very carefully because any variation in the efficiency of silencing (caused by variations in environment for instance) could result in an allergic reaction to a crop believed to be non-allergenic. The potential consequences of gene silencing need to be examined carefully during the regulatory risk assessment. Transgene silencing can be strongly influenced by environmental conditions such as light, temperature and nutrient availability and agronomic practices such as seedling transplantation (Brandle, 1995; Down 2001). It may not be possible to investigate all such scenarios in laboratory or field studies. The changes seen between growth chamber, greenhouse and field also indicate that extrapolation from one environment to another is not always possible.

There can be variation in the expression of transgenes in different parts (e.g. leaf, root, flower) of GM plants (tissue specificity). The expression of transgenes is controlled by tissue specific promoters or gene switches. Many of the early transgenes introduced into plants were regulated by constitutive promoters (e.g. the 35S promoter from cauliflower mosaic virus) which expressed in most tissues of the plant. However, there is now a move to more specific gene promoters. It is usual, however, to see variation between different independently transformed plants in the expression of transgenes using a tissue specific promoter. This is understood to result from 'position effects' i.e. the expression of a gene is influenced by its position in the genome or its genetic context. The nature of tissue specificity is important for food, feed and environmental safety where there may be a need to target transgene expression to the edible or non-edible parts of crop plants or to particular growth stages. The targeting of transgene expression is considered case-by-case and is particularly important for characters such as pest resistance where non-target organisms might be adversely affected. In practice, this variation is addressed by analysis of tissue specificity during the assessment of transgenic plants and is an important requirement in regulatory risk assessment.

As with non-GM plant breeding, there is genetic variation between GM plants within a breeding programme. In practice this variation is used to select plants that express the GM character in the most desirable manner (tissue specificity, transgene expression levels etc). The further 'fine tuning' of a new GM variety also frequently includes the use of conventional non-GM breeding methods over several years of additional breeding and evaluation. The production of a commercially acceptable potato variety, for instance, requires attention to about 40 different crop characteristics, only one of which might been introduced by GM breeding. In a conventional, non-GM breeding programme, many thousands (or millions) of candidate plant lines are assessed to produce one line that has superior characteristics. The discard rate is particularly high for mutation breeding where the nature and extent of genetic change is undirected, and unpredictable. In the regulatory risk assessment it is possible to analyse GM plants with a degree of molecular precision impossible for most products of conventional non-GM plant breeding.

4.4 Is there general scientific agreement?

The widely accepted view within the biological research and plant breeding community is that there are many parallels in the properties of plants produced by GM and non-GM plant breeding methods. Indeed, there is a substantially greater discard rate from most conventional breeding methods than from GM methods. A detailed molecular understanding of gene position effects and gene silencing effects in GM plants is developing with current research. But both phenomena are also features of conventional (non-GM) genetics and breeding where it is rarely possible to study the molecular properties of unstable resident genes in any detail. It is also widely accepted that there is the potential for quite novel molecular interactions, which may fall outside our current scope of knowledge. There is extensive field testing and agronomic evaluation for non-GM breeding. GM crops are exposed to similar testing, but in addition include further testing on safety for animal and human health and for environmental impact under the European Union regulatory system. It is important that the tools available are sufficient. A major strand of scientific opinion considers the testing currently carried out in the EU to be robust and sufficiently comprehensive to provide GM crops that are at least as safe as conventional crops. This analysis is supported by practical experience in the cultivation and consumption of many millions of tonnes of GM crops internationally over eight years[9]. Another strand in scientific opinion considers that GM crops need to be grown, consumed and analysed for a longer period in order to justify drawing such a conclusion.

4.5 Is the issue unique to GM?

Unstable genes have been known and exploited in conventional breeding since the early days of genetics studies last century.

Tissue culture-induced procedures are used in the majority of crop genetic modification procedures. Tissue culture induced genetic variation has been used as a source of variation for non-GM plant breeding and the range of genetic variation obtained from this source has been described extensively. Tissue culture (or micro propagation) is also a common way to increase the numbers of plants ‘uniformly’ through vegetative propagation.

Insertion mutation is caused by naturally occurring mobile genes (transposons). They have the potential to mutate genes throughout the plant genome. Mutation occurs from many other sources in the genome and is the origin of differences between all genes on which genetic recombination and natural selection can act. These are the essential requirements for evolution.

A much higher discard rate is common in conventional breeding than for GM plant breeding, reflecting undesirable, unpredicted or genetic events. The success of breeding relies heavily on the identification of desirable plants from a wide range of genetically different breeding lines. In

[9] The vast majority of crop varieties providing the foods we eat have never been tested formally or safety. In these instances safety is established by use. GM crops and foods pass through an extensive regulatory assessment as required under EU Directives.

many cases, transgenic lines are used as a source of new genes for further breeding by non-GM methods over several years.

A special feature of GM breeding is that it allows the transfer into crop plants of one or a few genes from what might be radically different organisms. Conventional breeding cannot, for example, form plants that can assemble complex human immunoglobulins as has been achieved in GM plants (see Ma *et al.* 1995). This inevitably raises uncertainty about whether there are any novel genetic interactions and whether these are potentially harmful (Lim *et al.* 2002). To determine definitively the relative scale of the uncertainties would require scientific investigation of a kind that has only recently begun (Pawlowski and Somers 1996; Wang *et al.* 1996, Labra *et al.* 2001; Sala *et al.* 2000) and for which there are no firm general results. As a result, this issue can only be approached on a case-by-case basis.

A further special feature of GM breeding is that the products of particular gene constructs may become present in radically different foodstuffs, effectively independently of any biological relationships (Firn and Jones, 1999; Schubert 2002) As is discussed later in this report (Chapter 5.4), this can hold important implications for risk management policy in areas such as the avoidance of exposures to any allergens that might pass through regulatory screening.

4.6 Are there gaps in our knowledge or scientific uncertainties and are these important?

Conventional plant breeding can produce gross undirected and unpredictable genetic changes and in that sense has considerable uncertainty. This is well documented and we know much about the types of change at a cellular level (see quality of evidence). Plants with undesirable characters or performance are discarded in the assessment stage of a breeding programme, so that only those plant genotypes that perform well over several sexual generations (progeny testing) and in different environments are accepted.

However, as has already been noted above, the GM process does introduce certain novel sources of uncertainty. The degree of uncertainty is related to our ability to detect and interpret changes at a molecular level. Our ability to do this relies on the tools that are available. GM plant breeding has not developed in isolation and it is possible to analyse the products with a degree of molecular precision that is not possible in non-GM methods of plant breeding.

For assessment of the future potential impacts of GM crops, it is especially important to gain a better understanding of the: (a) Genetic interactions associated with gene stacking; (b) Mechanisms of genome evolution and the induction of new variation within the genome (c) the biochemical implications of introducing familiar enzymes under the control of novel systems (e.g. EPSPS under the control of the CaMV 35S promoter) and the implications to the host of introducing novel enzymes.

4,7 Likely future developments

There is research on targeting transgene constructs to particular regions in the plant genome (already common in micro-organisms, lower plant forms such as the mosses and higher plant plastids by homologous recombination) as part of the transformation process. It has been claimed that this could reduce the variation between independent transgenic plants in transgene expression caused by position effects. The early indications from this research suggest that there is still variation in levels of expression when targeting is achieved in higher plants. It will probably still be necessary to produce several transgenic plants and test them for desirable performance (Ow, 2002).

There is likely to be an increase in the range of plant promoters to achieve more targeted transgene expression to particular plant tissues. This is a potentially valuable development for targeting transgene expression to edible or non-edible parts of plants. The use of less familiar gene promoters will mean that tissue specificity of transgene expression will need to be analysed carefully as part of any regulatory risk assessment (Topping and Lindsey, 1995).

There will be increased concentration on the regulation of endogenous gene expression using transgenic methods, including the utilisation of gene-silencing constructs. Underpinning research on factors affecting gene silencing will be important for risk assessment in applications of this kind (Grierson *et al*. 1996).

4.8 Where there is important scientific uncertainty, what is the potential way forward?

There is extensive research on molecular profiling methods to complement the current analysis of GM plants. This is a challenging area of research because plants from non-GM breeding programmes show genetic and phenotypic variation. Plants are also ‘plastic’ in that they respond and adapt to different environments by adjustments in expression of their genes. The challenge in this research will be to assess the significance of a change made by a genetic modification against existing substantial variations in background gene expression.

It would be valuable to gain a better understanding of the mechanisms of genome evolution to be able to see how genomes change under selection and during speciation. It would also be helpful to have a better understanding of epi-genetic phenomenon and their effect on gene expression. This topic is the subject of a number of current research programmes.

It is important that in the UK, we have regulatory oversight that is proportional to the degree of risk and the nature and scale of the uncertainties, and, which recognises the context and reference baseline provided by conventional breeding.