

Genetically modified plants for food use and human health—an update



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Preparation of this report

In 1998 the Royal Society issued the report *Genetically modified plants for food use*. The Society periodically issues updates on reports (recent examples include updates on bovine spongiform encephalopathies and stem cells) and the following update, which is based on research published in the last three years, specifically addresses human health aspects of genetically modified foods and the principle of substantial equivalence. The statement has been prepared by a working group chaired by Professor Jim Smith FRS (Wellcome CRC Institute, Cambridge). Other members are Dr Eric Brunner (Dept of Epidemiology and Public Health, University College London), Professor Douglas Fearon FRS (Wellcome Trust Immunology Unit, University of Cambridge), Dr Edward Holmes (Dept of Zoology, University of Oxford), Professor Alan Jackson (Institute of Human Nutrition, University of Southampton), Professor Chris Leaver FRS (Dept of Plant Sciences, University of Oxford), Professor Tom Meade FRS (MRC Epidemiology and Medical Care Unit, St Bartholomew's and the Royal London School of Medicine and Dentistry), Dr Clare Mills (Institute of Food Research, Norwich), Professor David Sherratt FRS (Dept of Biochemistry, University of Oxford), Professor David Walker FRS (Dept of Animal and Plant Sciences, University of Sheffield) and Dr Josephine Craig, Dr Rebecca Bowden and Mr Bahader Singh (Secretariat, Royal Society). This report has been endorsed by the Council of the Royal Society.

Summary

- 1 In 1998 the Royal Society published a report, *Genetically modified plants for food use*, which concluded that the use of genetically modified (GM) plants had the potential to offer benefits in agricultural practice, food quality, nutrition and health, but that there were several aspects of GM technology that required further consideration. The Royal Society appointed a group of experts to update this report based on research since 1998. This update focuses on the effects that GM foods might have on human health and the use of the principle of substantial equivalence in GM food safety testing.
 - 2 Few, if any, GM food products are currently available to buy in Europe and the UK. Commercial varieties produced elsewhere, in the USA and Canada for example, are designed to confer resistance to pests and to produce tolerance to specific herbicides. Over the next decade biotechnology will be aimed at improving many qualities of crops, including nutrition and agronomic performance. We support the continuation of research in this area as valuable in itself and as the only way to assess the true potential of GM plants.
 - 3 We endorse the conclusions of the 21st report of the Royal Commission on Environmental Pollution (1998) that scientific assessments must inform policy decisions but cannot pre-empt them, and that public opinion must be taken into account throughout. We believe that the public debate about GM food must take account of wider issues than the science alone. We also wish to stress the importance of informing debate with sound science.
 - 4 We have some concerns about the regulatory processes governing the development and use of GM plants. We agree with the FAO/WHO 2000 report that the criteria for safety assessments should be made explicit and objective and that differences in the application of the principle of substantial equivalence, for example in different Member States of the European Union, need to be resolved. We welcome the development of consensus documents by the OECD¹ for different crops so that the principle of substantial equivalence can be applied uniformly. It may not be necessary or feasible to subject all GM foods to the full range of evaluations, but those conditions which have to be satisfied should be defined.
 - 5 In the future safety assessments of GM and non-GM foods could make use of various new profiling techniques. Long-term research is required before these techniques can be applied. We recommend that
- research should continue to develop such technologies and thereby define the 'normal' compositions of conventional plants. We welcome the funding initiatives already put in place by the European Union Framework V programme and the UK's Food Standards Agency. Collaboration between the chemical industry, academia and regulators to develop techniques and share reference data will help ensure that agreement is reached on interpretation of results and use of new technologies.
- 6 One potential application of GM technology is to improve the nutritional quality of crops. It is possible that GM technology could lead to unpredicted harmful changes in the nutritional status of foods (MRC, 2000). Such alterations might also occur in the course of conventional breeding. Nutritional assessments are made as part of the safety assessment of GM crops, but more detailed guidelines would be beneficial. Vulnerable groups such as infants need special guidelines. To date no GM food for use in infant products has been submitted for approval. Detailed guidelines and legislation already exist for infant formulas and follow-on foods but it is not clear how they interact with GM food regulations. Therefore we recommend that both the Government and the European Commission should ensure that these two sets of regulations are complementary. Guidelines such as those described by COMA (1996) for nutritional assessment of infant formulas and more recently by Aggett *et al.* (2001) should be adopted for both novel and GM foods.
 - 7 There is at present no evidence that GM foods cause allergic reactions. The allergenic risks posed by GM plants are in principle no greater than those posed by conventionally derived crops or by plants introduced from other areas of the world. One shortcoming in current screening methods, which applies to both conventional and GM foods, is that there is no formal assessment of the allergenic risks posed by inhalation of pollen and dusts. We therefore recommend that current decision trees be expanded to encompass inhalant as well as food allergies.
 - 8 Plant viral DNA sequences are commonly used in the construction of the genes inserted into GM plants, and concern has been expressed about this. Having reviewed the scientific evidence we conclude that the risks to human health associated with the use of specific viral DNA sequences in GM plants are negligible.
 - 9 One concern associated with GM foods is the possibility that genes introduced into GM plants might become incorporated into the consumer's genetic make-up. Since the Royal Society's 1998 report various

¹ <http://www.oecd.org/oeecd/pages/home/displaygeneral/o,3380,EN-document-52814-no-27-9461-528,ff.html>

papers have been published on this topic. The results need to be viewed in the context of a normal diet, which for humans and animals comprises large amounts of DNA. This DNA is derived not only from the cells of food sources, but also from any contaminating microbes and viruses. Given the very long history of DNA consumption from a wide variety of sources, we conclude that such consumption poses no significant risk to human health, and that additional ingestion of GM DNA has no effect.

1 Introduction

The Royal Society report, *Genetically modified plants for food use* (1998), concluded that the use of genetically modified (GM) plants potentially offered benefits in agricultural practice, food quality, nutrition and health, but that there were several aspects of GM technology which required further consideration. We recognise that there is public concern about GM technology, particularly with respect to the safety of GM food for human consumption and to the possible effects of the technology on the environment. Since the 1998 report there has been new research which the working group has evaluated. This update focuses on the effects that GM foods might have on human health and the use of the principle of substantial equivalence in GM food safety testing. We plan to review developments on the environmental aspects of GM crops at a later date.

The 1998 report provides the background for this update, but we will redefine some of the key terms and issues at this point. Mankind has cultivated plants for thousands of years, during which time crop plants have continually been selected for improved yield, growth, disease resistance or food characteristics. The improvement of a plant species by 'conventional' techniques involves the selection for breeding purposes of certain plants that express desired characteristics. Plant breeders use sexual and asexual reproduction (including crosses between different species of plants) and other techniques (such as embryo rescue² and irradiation or chemical mutagenesis) to develop new plant varieties. Genetically modified plants differ from their conventional counterparts in that they are created by the deliberate insertion of specific genetic material using recombinant DNA technology. This technology may allow plant breeders to develop new varieties of crops at a faster rate than by conventional means, and it also allows the introduction of genetic material from other species, families or even kingdoms, which in many cases is not possible by conventional means. More specifically it allows the introduction of single genes and modification of a specific trait. Custers (2001) provides an overview of the techniques used in

both conventional breeding and genetic modification. Recently the role of GM plants in world agriculture has been considered by seven national academies including the Royal Society (*Transgenic plants and world agriculture*, Royal Society, 2000). The report concludes that the real potential of GM technology to help address some of the most serious concerns of world agriculture has only recently begun to be explored. Although GM technology has not yet developed to the point that a wide variety of GM crops is available, commercially produced varieties in countries such as the USA and Canada include GM crops that are designed to confer resistance to insect pests and to produce tolerance to specific herbicides (James, 2000). One significant effect of these measures might be a reduction, both quantitatively and qualitatively, in the use of pesticides (see Royal Society, 2000 for further details). Over the next decade biotechnology will aim to improve the nutritional qualities of crops and agronomic performance by targeting traits such as yield and stress tolerance. GM technology may therefore help meet the demand for food by an expanding world population with less impact on the environment. It is clear, however, that realisation of this potential will require continued development and evaluation.

At the start of this study we issued a call requesting scientific evidence (Appendix 1) relating to the following human health aspects of GM foods:

- the use of the principle of 'substantial equivalence' in the safety assessment of GM foods
- possible effects of GM foods on human nutrition
- possible effects of GM foods on allergic responses
- potential effects on human health resulting from the use of viral DNA in plants
- the fate of GM plant DNA in the digestive system.

The organisations and people who responded are listed in Appendix 2. In addition to receiving written evidence, we invited the Advisory Committee on Novel Food and Processes, Friends of the Earth, Greenpeace, Monsanto, Syngenta and several individuals to present oral evidence to the Committee (Appendix 2). A record of this evidence is posted on the Royal Society's website (<http://www.royalsoc.ac.uk/policy/>).

Some respondents raised social and ethical concerns about GM technology. We have confined ourselves to commenting on the scientific issues involved in genetic modification of plants because this is where our expertise lies. Social and ethical concerns have been discussed by the Food and Agriculture Organisation/World Health Organisation (FAO/WHO, 2001b), the Nuffield Council on Bioethics (1999) and the Church of Scotland.³ The seven

² see glossary in appendix 5 for 'embryo rescue' and other technical terms

³ <http://www.srtp.org.uk>

academies report (Royal Society, 2000) *Transgenic plants and world agriculture*, which is aimed specifically at developing countries, addresses issues relating to food security such as intellectual property.

In June 1999, the Royal Society published a report, *Review of data on possible toxicity of GM potatoes*, in response to claims made by Dr Pusztai (Ewen & Pusztai, 1999). The report found that Dr Pusztai had produced no convincing evidence of adverse effects from GM potatoes on the growth of rats or their immune function. It concluded that the only way to clarify Dr Pusztai's claims would be to refine his experimental design and carry out further studies to test clearly defined hypotheses focused on the specific effects reported by him. Such studies, on the results of feeding GM sweet peppers and GM tomatoes to rats, and GM soya to mice and rats, have now been completed and no adverse effects have been found (Gasson & Burke, 2001).

We endorse the conclusion of the 21st report of the Royal Commission on Environmental Pollution (1998) that 'scientific assessments, and analyses of technology, economics, risk and implementation issues, must inform policy decisions but cannot pre-empt them. Setting a standard or target is a practical judgement which has to be made in the light of all relevant factors. People's values must be taken into account throughout, beginning at the stage of defining a problem and framing the questions that need to be addressed'. Thus we believe that the public debate about GM food must take account of wider issues than the science alone, but we wish to stress the importance of informing debate with sound science.

2 The use of substantial equivalence in the safety assessment of GM food

In 1993, anticipating the need to develop a means of assessing the safety of GM foods, the Organisation for Economic Co-operation and Development (OECD) published the findings of a working group, which introduced the principle of 'substantial equivalence'. Substantial equivalence is based on the principle that if a novel or GM food can be shown to be essentially equivalent in composition to an existing food then it can be considered as safe as its conventional equivalent. This principle, which was endorsed by a joint FAO/WHO consultation in 1996, also recognises that foodstuffs represent highly complex mixtures of many different compounds and that the detailed composition and nutritional values of many crops will depend, among other things, on growth conditions, climate, and time of harvesting. It also recognises that toxicological testing of whole foods has limitations due to bulkiness (the difficulties in ingesting sufficient quantities of the whole

food in the diet) compared with food additives or medicines. Indeed, application of such tests to many conventional crops with a 'history of safe use' may cause them to be defined as unsafe.

In recognition of these difficulties, the principle of substantial equivalence requires that GM plants be assessed by comparing the GM plant with its conventional counterpart. In scientific language, the conventional crop is regarded as the control. The FAO/WHO report (1996) identifies three possible outcomes of such an evaluation, which then are used to structure the safety assessment required for a particular GM product.

First, the GM foodstuff might be regarded as substantially equivalent to its conventional counterpart both toxicologically and nutritionally. An example of a foodstuff recognised to be substantially equivalent to its conventional counterpart is oil derived from a GM plant such as maize or soya, as it does not include detectable protein or DNA derived from the GM plant. When a product has been shown to be substantially equivalent, no further safety assessment is required.

Second, it might be substantially equivalent apart from certain defined differences. Sometimes the GM food product includes the components deliberately introduced by genetic modification. In this case the GM food product might be regarded as 'substantially equivalent to its conventional counterpart except for a small number of clearly defined differences'. Assessment is then limited to examining the implications of the difference(s), perhaps by testing the novel components of the GM plant in isolation.

And third, the GM product might be regarded as not substantially equivalent to its conventional counterpart, or there might not be a suitable reference available for comparison. The product will then need a highly detailed safety assessment.

At present, safety evaluations include detailed consideration of the genetic modification procedure with respect to both the DNA sequences that are introduced and the site of their integration in the genome of the parent plant. Phenotypic data and detailed chemical composition data covering a wide range of nutritionally important parameters are usually considered, as well as an assessment of the allergic potential arising from foreign DNA (transgenes) in GM foods.⁴ If there are differences between the GM product and its conventional counterpart, then further investigations are carried out. These may include toxicology assessments (for example of the introduced protein) and animal feeding studies.

The amount of comparative data required to establish substantial equivalence involves a somewhat subjective

⁴ A summary of current EU legislation is given in Appendix 3

judgement (Medical Research Council (MRC) report, 2000) and thus has been questioned. We believe that at present there is no evidence to suggest that those GM foods that have been approved for use are harmful. Nevertheless, the principle of substantial equivalence has been the subject of considerable criticism and comment (Royal Society of Canada, 2001). In particular, it has been argued that the approach is subjective and inconsistent and even that it represents 'pseudo-science' (Millstone *et al.*, 1999). It has been suggested that the principle was introduced to provide an excuse for not carrying out the appropriate toxicological tests. One particular concern has been that the application of substantial equivalence may not reveal any unexpected effects of genetic modification. For instance, the introduction of a gene (or, especially, of multiple genes) into a plant species may cause there to be a presence, perhaps at very low levels, of previously unknown toxins, anti-nutrients or allergens. This controversy was recognised in a second FAO/WHO report in 2000, which referred to the 'mistaken perception that the determination of substantial equivalence was the end point of a safety assessment rather than the starting point'. It went on to recommend ways in which substantial equivalence might best be applied in the future, including, as we discuss below, animal testing, profiling techniques, nutritional analyses and allergenicity testing.

We accept that it is usually not feasible to evaluate the safety of genetically modified foods by the standards applied to certain food additives or medicines (MRC, 2000). Some form of 'substantial equivalence', starting with a direct comparison of the novel foodstuffs with their unmodified counterparts, appears to be the only practical solution. We agree with the 2000 FAO/WHO report, however, that the criteria for safety assessments should be made explicit and objective and that differences in the application of substantial equivalence, for example in different Member States of the European Union, need to be resolved (OECD, 2000). We welcome the development of consensus documents for different crops by the OECD which will help to facilitate the uniform application of substantial equivalence. We recommend that potential effects of the transformation process should continue to be taken into consideration in the safety assessment, and that the phenotypic characteristics to be compared between foods derived from GM plants and their comparators should be defined. These will include, but may not be limited to, composition, nutritional value, allergenicity and toxicity. It will be important to define the choice of growing conditions of the comparative plants, the scope of the comparisons, and the acceptable margins of measured differences in composition. It may not be necessary or feasible to subject all GM foods to the full range of evaluations, but those conditions which have to be satisfied should be defined.

In the future, safety assessments might make use of new profiling techniques such as micro-array technology for detailed studies of mRNA expression, quantitative two-dimensional gel electrophoresis and mass spectrometry for protein analysis, and metabolomic analyses to look at changes in all metabolites and metabolic intermediates. Application of such techniques to characterise differences between the GM crop and the appropriate comparator should help provide a rigorous scientific basis for hazard identification. However, much development work remains to be done, in particular to determine the utility of this approach in relation to the wide natural variation in composition between crops grown in different environments. Long-term research is required before these techniques can be applied to safety assessments of GM and non-GM foods. We recommend that research should be undertaken to develop such technology and to define the 'normal' compositions of conventional plants. We welcome the funding initiatives already put in place by European Union Framework V programme and the UK's Food Standards Agency (FSA). We also recommend that the biotechnology industry collaborate with academia and regulators to develop techniques and share reference data. This will help ensure that the new techniques are wisely applied and that agreement is reached on interpretation of results.

As with genetic modification, conventional plant breeding technology (which can involve chemical or radiation-induced mutagenesis or cross-species hybridisation) might also cause rearrangements of the genome, and therefore might also cause the activation of previously unknown toxins, anti-nutrients or allergens. Examples, though uncommon, include an insect-resistant line of celery proved to accumulate psoralen in response to light and thereby cause skin burns (Ames and Gold, 1999), and the Magnum Bonum potato line which accumulated toxic levels of solanine in cool weather (Van Gelder *et al.*, 1988). This raises the question of whether the same safety assessment criteria should be applied to conventionally modified foods as to GM foods.

The feasibility and value of studies in humans to assess the health effects of GM foods have been considered by the MRC's expert group (2000). They concluded that the value of epidemiological studies in assessing the post-marketing effects on human health is limited. This is because there are no reasonably firm hypotheses about which human health end-points GM foods might affect, because individual exposure to GM foods will be difficult to assess, and because the level of consumption of GM foods at the present time is very low. Randomised controlled trials were considered to be feasible. Whilst these were not suggested as a routine method of assessing new foods, such studies could be used to satisfy public concern at least about the short-term health effects of individual GM foods of nutritional importance.

The Food Standards Agency has commissioned a two-year study to look at the feasibility of monitoring consumption of GM foods; results of this work are expected in 2003.

3 Possible effects of GM food on human nutrition

As described in the Introduction, one potential application of GM technology is to improve the nutritional quality of crops and thereby improve human health (for further information see MRC, 2000; Royal Society, 2000). In the commercial market at present there are no GM foods that are modified to enhance nutrition. Although GM technology offers the potential for beneficial changes in the composition of a food, such changes need to be considered within the context of the overall diet. Good health requires a balanced diet which contains all the essential nutrients in an optimal range of proportions. Studies of the effects of GM food on nutrition need to take account of the effects of small changes that might result from the consumption of a particular GM food in a balanced diet. Studies also need to be made of the potential health effects in sub-groups of the population that have particularly high intakes or particular susceptibilities. Although it is possible that genetic modification might lead to unpredicted and harmful changes in the nutritional status of the food, such changes might also occur in the course of conventional breeding (MRC, 2000).

Nutritional assessments are made as part of the safety assessment of a GM food. Guidelines have been issued by the European Commission Scientific Committee for Food (1997). The assessment reviews the composition of the novel food, its preparation, and the role it is expected to have in the diet. The novel food is compared to traditional counterparts and the significance of any differences is assessed; this may include the use of animal models to establish some aspects of nutritional quality. Full nutritional assessment may need to be made in human subjects. Nutritional implications are assessed at 'normal' and 'maximum' levels of consumption. Nutrient composition data take into account the effects of storage, further processing and cooking. Attention is paid to the particular physiological characteristics and metabolic requirements of vulnerable groups such as infants, children, pregnant and lactating women, the elderly and those with chronic disease.

Although vulnerable groups are mentioned in the European Commission's guidelines more detailed guidelines are required to cover experimental design, consider the form in which the food is provided, and consider the adequacy of the food in terms of energy and nutrients. Where necessary,

data from feeding studies should be included in the assessment. In animal studies, any changes in tissue structure or metabolic function of various organs (liver, kidney, lungs, brain and cardiovascular organs) should be assessed. In human studies, measures of general health, development and psychological well being should be included (see section 2). We recommend that, in the case of infants, guidelines such as those described by the Committee on Medical Aspects of Food and Nutrition policy (COMA, 1996) for nutritional assessment of infant formulas and more recently by Aggett *et al.* (2001) should be adopted for both novel and GM food. Labelling of novel foods that provides nutritional information and guidance for vulnerable groups is currently under consideration by the Advisory Committee on Novel Foods and Processes (ACNFP).

Products that are designed to be consumed as a single food over extended periods of time by those who are especially vulnerable should be investigated most rigorously. These include infant formulas and follow-on foods. Within the UK, infant formulas and follow-on foods are the responsibility of the Department of Health. To date no GM foods for use in infant products have been submitted for approval, but it is expected that approval of such foods would be referred via the ACNFP to the Scientific Advisory Committee on Nutrition.⁵ There is a lack of clarity about the interaction of regulations on infant foods and GM foods. This needs careful examination to ensure that these two sets of regulation are complementary and we recommend that the Government review the enforcement of these regulations. Commission Directive 91/321/EEC, which is currently under review by the European Commission, covers infant formulas and follow-on foods. We recommend that the Commission consider the use of novel and GM foods in infant foods as part of this review.

4 Possible allergic responses to GM foods

Food allergies occur in 1–2% of adults and 6–8% of children (Metcalf *et al.*, 1996; Sampson, 1997), although severe allergic reactions (anaphylaxis) to foods are relatively rare, occurring in approximately 3.2 individuals per 100,000 people per year (Burks and Sampson, 1997). As almost all known allergens are proteins, we restrict our discussion to protein products of GM plants and not, for example, to highly refined oils, which pose little allergenic risk because processing removes virtually all protein (Hourihane *et al.*, 1997).

The introduction of a new gene into a plant, or a change in the expression of an existing gene, may cause that plant to become allergenic. That is, it may induce allergic responses in individuals who are already hypersensitive to the allergen in question, or it may cause individuals

⁵ The Scientific Advisory Committee on Nutrition (SACN) replaced the Committee on Medical Aspects of Food and Nutrition (COMA) in 2001.

previously not allergic to the allergen to become so. Therefore known allergens should not be introduced into food crops and every effort should be made to avoid this. There is at present no evidence that GM foods that are commercially available cause any clinical manifestations of allergenicity, and assertions to the contrary have not been supported by systematic analysis (Center for Disease Control, 2001). The allergenic risks posed by GM plants are in principle no greater than those posed by conventionally-derived crops or by plants introduced from other parts of the world, such as the introduction of kiwi fruit into Europe. Nevertheless, it is important to consider potential allergenic risks posed by GM plants and to place them in the context of risks posed by introduced plants and plants produced by conventional or organic means. There are already examples of such risks from non-GM crops, such as allergens from fungal spores on mouldy hay, on cereal grains or on crops with high infestations of fungal pathogens (this may occur in crops not treated with an appropriate fungicide). These have been shown to be potent inducers of asthma resulting in a condition commonly known as farmer's lung.

Allergic sensitisation to a GM plant, as with a conventionally derived plant, could occur via the lungs (perhaps through inhaling pollen or dust created during milling) or through skin contact (for example, during handling), as well as via the gastrointestinal tract following ingestion of foods. Occupational allergies to conventional plants can take the form of either immediate hypersensitivity or delayed hypersensitivity reactions. The latter frequently occur as a consequence of handling plant materials and generally express themselves as contact dermatitis. Of immediate hypersensitivity allergies to plants, those that involve inhalation of particulates are particularly common. These include allergic diseases, such as baker's asthma which results from inhalation of flour particles, and latex allergy which is thought to arise from inhalation of the powder used to coat latex gloves (to which some latex from the gloves becomes associated). Those at risk from pollen include the general population and, in particular, farm workers. Individuals involved in the harvesting of crops and in food processing techniques that generate dusts are at risk of sensitisation through both inhalation and skin contact. Therefore, in order to adequately assess any risks, it is important to evaluate the allergenic potential of GM plants through inhalation and skin contact as well as via ingestion.

Decision trees for assessing the allergenic risks of GM foods have been developed by the International Food Biotechnology Council in collaboration with the International Life Sciences Institute (1996) and most recently by FAO/WHO (2001a). This hierarchical approach includes determining whether the source of the introduced gene is from an allergenic plant, whether GM foods react with antibodies in the sera of patients with

known allergies, and whether the product encoded by the new gene has similar chemical and biological properties to known allergens. It also involves animal models of allergy that can be used to screen genetically modified foods. Ongoing research to develop more adequate animal models for allergenicity testing will increase the assurance of this process still further. The current practice of screening described above means any food that is allergenic is unlikely to reach the market.

However, one shortcoming in current screening methods, which applies to conventional foods as well as to GM foods, is that there is no formal assessment of the allergic risks posed by inhalation of pollens and dusts. We therefore recommend that current decision trees be expanded to encompass inhalant as well as food allergies. In the longer term, should GM foods be re-introduced into the market in the UK, we suggest that the Food Standards Agency considers whether post-marketing surveillance should be part of the overall safety strategy for allergies, especially of high-risk groups such as infants and individuals in 'atopic' families. The collection of properly collated longitudinal public health data is one of the only ways to identify rare allergies, to any food, in the population. Whether such monitoring is feasible for GM food is not yet clear; it is discussed in section 2.

5 Potential effects on human health resulting from the use of viral DNA in plants

Two types of plant viral DNA sequence are commonly used in the construction of genes inserted into GM plants. The first includes 'promoters', usually short sequences of DNA that are required for the expression ('switching on') of all genes. In GM plants the inserted gene is often combined with a promoter derived from the cauliflower mosaic plant virus (the so-called CaMV 35S promoter). The second type of sequence comprises genes that encode the outer protective coat proteins of viruses, which when expressed in the host plant interfere with infecting viruses and confer resistance. However, to date no commercial GM crops using this second type of gene are grown.

It has been suggested that the introduction of viral DNA sequences into GM plants could produce new viruses through recombination ('gene exchange'), either with the remnants of viral DNA sequences that are commonly found in the genomes of all species or with naturally infecting plant and animal viruses. There are, however, natural barriers to this process (Aaziz & Tepfer, 1999; Worobey & Holmes, 1999). Most importantly, viruses generally infect a limited range of species and although there are genetic similarities between some viruses that infect plants and animals, suggesting that they may have jumped between these kingdoms in their evolutionary past, such events must be rare; the gene sequences of

plant and animal viruses are usually so dissimilar that plant viruses cannot infect animal cells. Indeed, there is only one reported case of recombination between a plant and an animal virus (Gibbs & Weiller, 1999) and although humans have eaten virally infected plants for millennia, there is no evidence that this has created new viruses by recombination or has caused serious disease. In the extremely unlikely case of recombination producing a novel virus, this would probably be defective, because most recombination events disrupt functional genes. These sub-optimal viruses would be removed from the population by natural selection, as is the case for most recombinant viruses produced naturally. Though unlikely, there is a potential risk that the use of complete viral genes to create transgenic plants resistant to viral infections may create new plant viruses. These novel recombinants could result in plant diseases but this process has not been documented to date.

Concern has been expressed over the use of the CaMV 35S promoter (Ho *et al.*, 1999; Ho *et al.*, 2000) because this functions in a wide variety of species, including some vertebrates, and has been shown to undergo recombination in laboratory studies (Kohli *et al.*, 1999; Morel & Tepfer, 2000). However, the promoter sequences used in GM plants are a normal constituent of common plant viruses that frequently infect food plants and there is no evidence that these sequences have been involved in the creation of new viruses. In the case of cauliflower mosaic virus (CaMV), studies have shown that 10% of cabbages and 50% of cauliflowers are infected with the virus (cited in Hull *et al.*, 2000) and CaMV has never been shown to cause disease in humans or to recombine with human viruses. It is also highly unlikely that the CaMV 35S promoter could reactivate the remnants of viruses that are integrated into the genomes of most species. Although there is a great variation among species, most integrated viruses are inert because they contain multiple mutations and cannot be reactivated by the simple acquisition of the CaMV 35S or any other promoter. In humans, approximately 1% of total DNA is composed of integrated viruses, but only one of these viruses, HERV-K, may be active (Turner *et al.*, 2001).

It has also been suggested that genetic modification may activate transposable elements already present in the human genome. Like viruses, transposable elements – short DNA sequences that have the ability to move around the genomes of eukaryotes and bacteria, increasing in number as they do so – have been commonly associated with host organisms since early in evolution. Because of their mobility, transposable elements have the ability to insert themselves into and thereby damage host genes and thus potentially lead to pathological effects such as tumours (Hiom *et al.*, 1998). These elements comprise up to 40% of the total DNA of higher animals and plants. There is strong evidence that transposable elements have repeatedly been transferred among different species during evolution (Capy

et al., 1994; Kidwell, 1993; Silva & Kidwell, 2000; Royal Society, 2001). Consequently, it seems improbable that the accidental mobilisation of transposable elements during the construction and use of GM plants would have any broad impact on the biology of humans, animals or plants compared with what takes place under natural conditions.

We conclude that the risks to human health associated with the use of specific viral DNA sequences in GM plants are negligible.

6 The fate of GM plant DNA in the digestive system

One concern associated with GM foods is the possibility that genes introduced into the plant might become incorporated into the consumer's genetic make-up. The Royal Society 1998 report concluded that there was no evidence for transfer of intact genes to humans either from bacteria in the gut or from foodstuffs, despite daily consumption of DNA in the diet. Since 1998 a number of papers have been published on this topic, and these are reviewed below.

Most ingested DNA is rapidly broken down in the intestinal tract (see Royal Society, 1998, section 3.4), although it can persist for some time in saliva (Schubbert *et al.*, 1994). Nevertheless, low levels of uptake of gene-sized DNA into cells of the gastrointestinal tract have been detected (Duggan *et al.*, 2000; Schubbert *et al.*, 1996; Doerfler, 2000; Einspanier *et al.*, 2001; Flachowsky, 2000). The uptake may be due to specialised cells of the lining of the gastrointestinal tract (so-called M-cells), which actively sample gut contents as part of the process of protecting the body from infection (Nicoletti, 2000). This will normally have no biological consequences because the DNA will be degraded in the cell. There have been no reports of transgenes detected in the cells of cows fed GM maize, although the presence of plant chloroplast genes, which are present at about 1000 times higher concentration than any transgene, could be detected (Einspanier *et al.*, 2001; Flachowsky, 2000). This suggests that DNA present in food can find its way into mammalian cells at some low frequency. In the unlikely event that the DNA is recombined into a host chromosome, the probability that it will exert any biological effect on that cell is very low. The likelihood of any biological consequence for the whole organism is even more remote. There is no obvious way that a cell with altered biological properties due to foreign DNA uptake could transmit this effect to other cells or affect the germ-line of the host organism.

Any untoward consequences of DNA consumption would probably be due to ingestion and transmission of intact autonomous genetic elements rather than to transfer of fragments of DNA. Such elements might include the

complete genomes of viruses or transposable elements, or large pieces of DNA from normal intestinal microbial flora. Indeed, there is strong evidence that gene transfer events of this sort have occurred during evolution (Kidwell, 1993; Capy *et al.*, 1994). In particular, transposable elements, which comprise a large part of the mammalian genome, have close relatives in distant genera, while some transposable elements derived from nematodes and insects have been shown to transpose following introduction into mammalian cells in the laboratory (Luo *et al.*, 1998; Schouten *et al.*, 1998). Uptake of fragments of transgenic DNA from genetically modified food should therefore be seen in the context of an ongoing biological process involving intact autonomous genetic elements, which has had no detectable negative consequences.

An alternative scenario might involve the entry of a novel DNA sequence into gastrointestinal microbial flora, where it would replicate and persist in its new host and deliver a product into its surroundings. This has occurred throughout mammalian evolution and has apparently had little biological consequence (Stanhope *et al.*, 2001). The use of antibiotic resistance genes as a marker for selection of GM plants has resulted in the concern that genes may be transferred into the bacteria present in the stomach of the consumer; this would make the bacteria resistant to antibiotics. This was discussed in the Royal Society 1998 report, where we supported the Government's advisory bodies in their conclusion that such markers should not continue to be used in the human or animal food chain.

All these observations need to be viewed in the context of a normal diet, which for humans and animals comprises large amounts of DNA. For example, a 600 kg cow is estimated to ingest about 600 mg of DNA a day (Beever and Kemp, 2000) and indeed digestion of DNA in the gastrointestinal tract may make a significant contribution to nutrition. This DNA will be derived not only from the cells of food sources, but also from any contaminating microbes and viruses. Given the very long history of DNA consumption from a wide variety of sources, it is likely that such consumption poses no significant risk to human health, and that additional ingestion of GM DNA has no effect. Consequently, it is unlikely that the ingestion of well-characterised transgenes in normal food and their possible transfer to mammalian cells would have any significant deleterious biological effects.

7 Conclusions and recommendations

We recognise the valuable potential and current impact of plant biotechnology on the quality of food and its importance in the development of new crops. We support continuation of research on GM plants as valuable in itself and as the only way to assess the true potential of GM

plants. However, the Royal Society recognises the concerns expressed with regard to the technology and believes that these should continue to be addressed through collaboration and dialogue between industrialists, public sector scientists, regulatory authorities and non-government organisations. It is important that the public debate about GM food takes account of wider issues than the science alone, but we wish to stress the importance of informing debate with sound science.

We agree with the FAO/WHO 2000 consultation that the criteria for safety assessments of GM foods should be made explicit and objective and that differences in the application of substantial equivalence, for example in different Member States of the European Union, need to be resolved (OECD, 2000). Therefore we welcome the development of consensus documents for different crops by the OECD, which will help to facilitate the uniform application of substantial equivalence. We believe that the risks to human health associated with the use of specific viral DNA sequences in GM plants are negligible. Given the very long history of DNA consumption from a wide variety of sources, it is likely that such consumption poses no significant risk to human health, and that additional ingestion of GM DNA has no effect.

We have the following recommendations.

- Safety assessments should continue to consider potential effects of the transformation process. The phenotypic characteristics to be compared between foods derived from GM plants and their conventional counterparts should be defined. It may not be necessary or feasible to subject all GM foods to the full range of evaluations but those conditions that have to be satisfied should be defined.
- Research should be undertaken to develop modern profiling techniques and to define the 'normal' compositions of conventional plants. The working group welcomes the funding initiatives already put in place by the European Union Framework V programme and the UK's Food Standards Agency (FSA).
- The biotechnology industry should collaborate with academia and regulators to develop and share suitable reference data sets. This will help ensure that the new technologies are wisely applied and that agreement is reached on the appropriate interpretation of the data that they will generate.
- The UK Government should review the enforcement of the regulations on infant foods and GM foods to ensure these regulations are complementary.
- The European Commission should consider the use of novel and GM foods in infant foods as part of its review of Directive 91/321/EEC that covers infant formulas and follow-on foods.
- The current decision trees used to assess allergy should

be expanded to encompass inhalant as well as food allergies.

- In the longer term, should GM foods be re-introduced into the market in the UK, we suggest that the Food Standards Agency considers whether post-marketing surveillance should be part of the overall safety strategy for allergies, especially of high-risk groups such as infants and individuals in 'atopic' families.

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Appendix 1 Press Release (Issued 13 March 2001)

The Royal Society is undertaking an independent study into human health issues surrounding GM plants for food use, it was announced today. In its widely acclaimed 1998 report *Genetically modified plants for food use*, the Royal Society found that the use of GM organisms has the potential to offer real benefits in agricultural practice, food quality nutrition and health. However it did find some uncertainties: 'The current system of relying on identification of known allergens in the GM plant, coupled with the reliance on "substantial equivalence", may result in potential allergenicity problems being impossible to predict if there are no data available on the substances in question, particularly since mechanisms of allergenicity are often poorly understood'. It recommended 'that any over-arching body analyses the current regulations, giving particular attention to consideration of whether long-term animal feeding studies are necessary to provide greater information on allergenicity or toxicity'.

Since the 1998 report there has been considerable new research, so the Royal Society is convening a working group of 10 scientists in order to update its 1998 report. The working group will advise on any policy implications and issue a report later this year. Dr Jim Smith FRS, the Chairman of the working group, said 'There has been much public concern and debate in the media about possible adverse health effects of GM food. The Royal Society wants to facilitate the debate on this issue by providing the public and policy makers with an up-to-date and independent overview of the scientific evidence in the area'.

The study will consider evidence that has been collected since the publication of the Society's last report in September 1998. We welcome submissions from interested parties who have scientific evidence they would like us to consider in our study by 3 April 2001. Evidence received by 3 April will be examined by the working group at its first meeting later in April. We aim to publish the report in late summer, so have a fairly tight timetable. If you would like to submit written evidence but cannot do so by 3 April, please let us know. We may also invite some of those submitting written evidence to present their evidence in person to the working group.

In the study the working group will look at:

- Potential risks to human health resulting from the use of viral DNA in plants
- Prospective implications for human nutrition
- Potential problems with allergenicity of GM plants for food use
- Fate of DNA in the digestive system
- The use of substantial equivalence in the risk assessment of GM food.

We welcome comments on any other issues to do with the human health aspects of GM plants not covered by the above that we should be considering at this time.

The Royal Society has issued several reports on GM plants for food use, including *Genetically modified plants for food use* (1998), *Review of data on possible toxicity of GM potatoes* (1999) and *Regulation of biotechnology in the UK* (1999).

References can be found in Section 8.

Appendix 2 List of respondees to the study

The following organisations and people responded to the call for evidence:

Academy of Medical Sciences
Anaphylaxis Campaign
Food Standards Agency
Friends of the Earth
Greenpeace
Institute of Science in Society
Medical Research Council
Monsanto
New Zealand Life Sciences Network
Royal College of Physicians
Scientists for Global Responsibility
Soil Association
Syngenta

Luke Anderson (e-mail respondent)
Professor Janet Bainbridge, University of Teeside,
Middlesbrough, UK
Dr Judy Carman, Flinders University, South Australia
Dr Patricia Elliot (e-mail respondent)
Dr Brian Fenton, Scottish Crops Research Institute,
Dundee, UK
Maurice Lex, Directorate-General European Commission,
Brussels, Belgium
Dr Ulrich Loening, Centre for Human Ecology, Edinburgh,
UK
Dr Mark Tepfer, Institut National de la Recherche
Agronomique-Versailles, France

In addition oral evidence sessions were conducted with:

Professor Janet Bainbridge, Chair of Advisory Committee
on Novel Foods and Processes (ACNFP)
Adrian Bebb and Peter Riley, Friends of the Earth
Camilla Beech, Biotechnology Regulatory Affairs,
Syngenta
Dr Andrew Cockburn, Director of Scientific Affairs
(Europe/Africa), Monsanto
Professor Mike Gale FRS, John Innes Centre, and Dr Bill
Angus, Nickerson's Seeds
Sue Hattersley, Food Standards Agency
Dr Erik Millstone, Reader in Science Policy at SPRU,

Appendix 3 Legislation

Legislation governing the regulation of genetic modification is set by the European Union and implemented at national level by individual national regulators.

At EU level, there are two directives, which cover release and marketing (Directive 90/220/EEC) and use in containment (Directive 90/219/EEC) of genetically modified plants. A new, updated Directive 2001/18/EC on the deliberate release of genetically modified organisms (GMOs) will come into effect in October 2002 and will introduce mandatory information to the public and general rules on mandatory labelling and traceability at all stages of the placing of GMOs on the market. Products which are not GM but are derived from GMOs are assessed for safety in accordance with the requirements of the EC Novel Foods Regulation (258/97) which sets out rules for authorisation and labelling of novel food products containing, consisting of or produced from GMOs.

Further to the updated Directive 2001/18/EC, new regulations on GMOs have been proposed recently (July 2001) by the European Commission and are currently under examination by the European Parliament and Council of Ministers. The proposed regulation on GM food and feed establishes detailed rules for labelling, replaces the existing approval procedures for GM foods and introduces for the first time specific rules for the approval and labelling of GM animal feed. In comparison with the labelling system already in place (foods consisting of or containing GMOs are required to be labelled), all foods produced from GMOs irrespective of whether there is DNA or protein of GM origin in the final product and all genetically modified feed will be labelled. Food produced with the help of enzymes from GM sources and food from animals fed GM feed will not require labelling. The proposal also acknowledges that adventitious contamination cannot be totally avoided and allows for GMOs that have been favourably assessed by the EU Scientific Committee, but not yet fully approved, to be present in food or feed up to a maximum of 1%. The Commission's proposal places the new European Food Authority, rather than individual Member States, at the centre of the approval process, but Member States will take the final decisions on applications. The proposed regulation on GM traceability and labelling aims to elaborate on the requirements in Directive 2001/18/EC to trace live GMOs, and to extend them to derived products throughout the supply chain.

In the UK, the Genetically Modified (Contained Use) Regulations 2000 require all work with GM plants to be subject to a risk assessment for effects on human health and safety. As part of this, the GM plant is assessed on the basis of whether it is more likely to cause harm to humans than the non-modified parental organism. Any plant that poses a greater risk of harm to human health and safety than the non-modified equivalent must be notified to the Health and Safety Executive under the Genetically Modified (Contained Use) Regulations 2000 before work can commence. The Environmental Protection Act 1990 (EPA1990) requires risk assessment of all GMOs. The Genetically Modified Organisms (Risk Assessment) (Records and Exemptions) Regulations 1996 are made under the EPA1990. The EPA1990, together with the associated Regulations, requires that anyone keeping GM plants must carry out an assessment of the risks to the environment. The assessment must include hazards arising from the escape of the plants, and the risk of such hazards occurring. The assessment enables the keeper of the GM plant to put in place suitable containment measures to minimise damage to the environment resulting from escape.

GMOs may not be released into the environment unless they have received consent under the Genetically Modified Organisms (Deliberate Release) Regulations 1992 (as amended 1995 and 1997). Applications for consent must describe the GMO, and give details of the proposed release, and must contain a full risk assessment. Applications are submitted to the Department of Environment, Food & Rural Affairs (DEFRA), and reviewed by both DEFRA and other Government departments. Each application is also reviewed by an independent committee of experts, the Advisory Committee on Releases to the Environment (ACRE). ACRE conducts environmental risk assessment ensuring compliance with EC Directive 90/220/EEC by reviewing all applications to release and market GMOs.

The Food Standards Agency (FSA) is responsible for all aspects of the safety of GM foods. It is the UK foods competent authority, and therefore the UK body directly responsible for the approval of all novel foods, under the Novel Foods Regulation (EC Regulation 258/97). It is assisted in this by the Advisory Committee on Novel Foods and Processes (ACNFP), an independent body of experts containing consumer representatives that assesses the safety of novel foods and processes used in food production. The safety assessment is based on the concept of substantial equivalence, which involves a comparison of a GM food with its conventional equivalent and a detailed examination of any differences. There are a number of other expert bodies, which advise the FSA, for example, advice on food labelling is provided by the Food Advisory Committee (FAC) and advice on toxicology by the Committee on Toxicology (COT).

Appendix 4 Recommendations from the Royal Society 1998 report *Genetically modified plants for food use*

Recommendation	Current position
<p>Antibiotic resistance markers, if used in future, should be removed at an early stage in development of the GM plant, and where possible, alternative marker systems should be used.</p>	<p>In 1998 the Government's advisory committees on GM crops (the Advisory Committee on Releases into the Environment (ACRE) and the Advisory Committee on Novel Foods and Processes) had both made recommendations to this effect.</p> <p>The ACRE guidelines on Best Practice in GM crop design discuss the alternative marker systems available. http://www.defra.gov.uk/environment/acre/bestprac/guidance/index.htm</p>
<p>We strongly support mechanisms by which consumers can be informed about developments in biotechnology, including the labelling of foods containing GM material where the equivalence of a food is substantially changed, according to established criteria and provided such labelling is appropriately monitored. We recommend that the Government departments continue to work with the European Commission and all interested parties towards increased clarity in the labelling regulations.</p>	<p>New rules on labelling and tracing of GMOs have recently been proposed by the European Commission (25 July 2001). The new system meets the requests by Member States Governments, the European Parliament and consumer organisations, and has been drafted in close dialogue with all stakeholders and Member States. The proposals are subject to co-decision with the European Parliament and Council and should enter into force in 2003 at the latest. These rules will provide consumers with information by labelling all food and feed consisting of, containing or produced from a GMO. The labelling provisions in respect of food and feed will be reviewed after two years of operation. http://europa.eu.int/comm/food/index_en.html</p> <p>However the UK's Food Standards Agency (FSA) has criticised these proposals; it is not convinced they are enforceable, practical and affordable. Instead the FSA suggests maintaining the current labelling rules but supplementing these with the introduction of a provision of 'GM-free' labelling. http://www.foodstandards.gov.uk/press_releases/statements/st010921.htm</p>
<p>We recommend that an over-arching body or 'super-regulator' should be commissioned by the Government to span departmental responsibilities and have an ongoing role to monitor the wider issues associated with the development of GM plants. In addition, the proposed Food Standards Agency might have a role to play.</p>	<p>In 1999 the Government reviewed its advisory and regulatory framework on biotechnology. It concluded that a broader approach was needed for strategic issues. The Agriculture and Environment Biotechnology Commission (AEBBC) forms part of the new strategic framework. It will look at the broad picture taking ethical and social issues into account as well as the science. The Commission will offer strategic advice to Government on biotechnology issues which impact on agriculture and the environment. It will liaise closely with but not duplicate the work of the FSA which includes within its responsibilities all aspects of the safety and use of genetically modified food and animal feed. http://www.foodstandards.gov.uk/index.htm http://www.aebc.gov.uk/aebc/index.htm</p>

Recommendation	Current position
<p>We recommend that the current regulations are analysed, with particular attention to whether allergenicity and toxicity of GMOs receive adequate consideration</p>	<p>The Medical Research Council report on GM foods (MRC, 2000) concluded that mechanisms of food allergy should be the subject of further research and that this would facilitate the design and development of novel approaches for the identification and characterisation of potential protein allergens. The MRC has called for research proposals on food allergenicity in relation to GM foodstuffs. http://www.mrc.ac.uk/gmfood.html</p> <p>A FAO/WHO Expert Consultation evaluated allergenicity of GM foods in January 2001 (FAO/WHO, 2001a). A new decision tree for assessment of allergic potential of foods has been suggested. In addition the consultation concluded that further research is needed on the development and validation of suitable animal models and procedures for the assessment of allergenicity of foods derived from biotechnology. http://www.fao.org/es/ESN/gm/allergygm.pdf References can be found in Section 8.</p>

Appendix 5 Glossary

		Genome	the entire chromosomal genetic material of an organism
Allergen	any substance that causes an allergic reaction.	Metabolomic	the study of the complement of metabolites present in a single cell/tissue under specified conditions
Anaphylaxis	an acute allergic reaction of tissue due to exposure to a previously encountered allergen	Mutagenesis	the process of an agent promoting mutation
Atopic	pre-disposition to allergic response, usually inherited	Phenotypic	the appearance or other characteristics of an organism, resulting from the interaction of its genetic constitution with the environment
Chromosome	a large DNA molecular chain in the cell along which genes are located	Promoter	a region of DNA involved in binding the enzyme that synthesizes RNA from the DNA
DNA	deoxyribonucleic acid, which is present in almost all living cells and contains information coding for cellular structure, organisation and function	Recombination	the rearrangement, for example by crossing over, of nucleic acid molecules to produce new sequences
Embryo rescue	two species which would not naturally hybridise are crossed, thereby resulting in a non-viable embryo. The embryo is removed from the plant and allowed to develop further <i>in vitro</i>	RNA	ribonucleic acid; similar in structure to DNA, plays an important role in protein synthesis and other chemical activities of the cell. Many viruses are composed entirely of RNA
Eukaryote	an organism having cells each with a nucleus within which the genetic material is contained. The cells of higher plants, animals, fungi, protozoa and most algae are eukaryotic	Transgenic	adjective describing an organism in which a foreign DNA gene (a transgene) is incorporated into its genome
Expression	not all genes are active. When a gene is read and the product of the gene (always including RNA and usually a protein) is produced, the gene is said to be expressed	Transposable element	small piece of DNA carrying a gene and other information, that allows it to integrate into many chromosomal positions within the genome
Gene	the basic unit of heredity; an ordered sequence of nucleotide bases, comprising of a segment of DNA. A gene may contain the sequence of DNA that encodes one protein chain		

The following online dictionaries contain further definitions of terms:

<http://www.fao.org/DOCREP/003/X3910E/X3910E00.htm>

<http://www.hon.ch/Library/Theme/Allergy/Glossary/allergy.html>

<http://www.sciencekomm.at/advice/dict.html>

Other recent Royal Society reports

Response to the Policy Commission on the future of farming and food. (4 page response to the Policy Commission, 22/01, October 2001)*

Response to the consultation on DEFRA's aims and objectives. (2 page response to DEFRA consultation, 21/01, September 2001)*

Royal Society response to PIU Energy project scoping note. (5 page response to cabinet office consultation, 20/01, September 2001)*

The role of land carbon sinks in mitigating global climate change (2 page summary, 11/01, July 01, ISBN 0 85403 561 3 and 32 page document, 10/01, July 01, ISBN 0 85403 562 1)*

European Commission's white paper 'Strategy for a future chemicals policy' (5 page response to the inquiry by the House of Lords European Union Committee, 19/01, July 2001)*

The second stage of the quinquennial review of the Research Councils (17 page response to OST consultation 13/01, July 01)*

Draft code of practice for scientific advisory committees (3 page response to OST consultation 14/01, July 01)*

Investigating the use of animals in scientific research (3 page response to call for evidence by the House of Lords Animals in Scientific Procedures Committee, June 2001 Professor PPG Bateson FRS)*

Stem cells research-second update (4 page response to the inquiry by the House of Lords Science and Technology Committee 09/01, June 2001 ISBN 0 85403 560 5)*

Transmissible spongiform encephalopathies (11 page statement 08/01, 5 June 2001)*

The health hazards of depleted uranium munitions, Part 1(88 page document 06/01,22 May 2001, £17.50 ISBN 0 85403 3540)*

The health hazards of depleted uranium munitions, Part 1(2 page summary 07/01,22 May 2001)*

The use of genetically modified animals (46 page document 05/01, 21 May 2001, ISBN 0 85403 556 7)*

The Science of Climate Change (2 page joint statement from 16 scientific academies, 17 May 2001)*

Quinquennial Review of Royal Botanic Gardens, Kew (4-page response to MAFF's public consultation, document 04/01, submitted 6 April 2001)*

Genetics and Insurance (4-page response to the inquiry by the House of Commons Science and Technology Committee, 03/01, March 2001)*

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