Thirteenth report : the release of genetically engineered organisms to the environment / Royal Commission on Environmental Pollution ; Chairman Lord Lewis of Newnham.

ROYAL COMMISSION

ON

ENVIRONMENTAL POLLUTION

CHAIRMAN:
THE RT HON THE LORD LEWIS OF NEWNHAM

THIRTEENTH REPORT

THE RELEASE OF GENETICALLY ENGINEERED ORGANISMS TO THE ENVIRONMENT

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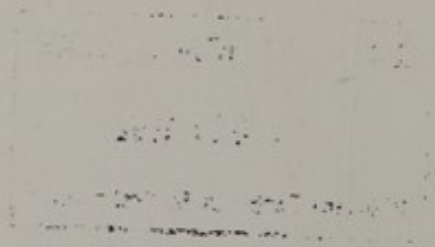

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ROYAL COMMISSION
ON
ENVIRONMENTAL POLLUTION

THIRTEENTH REPORT

To the Queen's Most Excellent Majesty

MAY IT PLEASE YOUR MAJESTY

We, the undersigned Commissioners, having been appointed "to advise on matters, both national and international, concerning the pollution of the environment; on the adequacy of research in this field; and the future possibilities of danger to the environment";

And to enquire into any such matters referred to us by one of Your Majesty's Secretaries of State or by one of Your Majesty's Ministers, or any other such matters on which we ourselves shall deem it expedient to advise:

HUMBLY SUBMIT TO YOUR MAJESTY THE FOLLOWING REPORT.

'Governmental action to guard against possible environmental disaster has never turned out to be either premature or unnecessary.'

Lord Zuckerman
Member of the Royal Commission 1970–1974

House of Lords Official Report, 20 October 1988. Column 1313

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CHAPTER 1

INTRODUCTION

Benefits and risks

1.1 This Report is about the environmental issues raised by the release of genetically engineered organisms (GEOs). 'Organism' is an omnibus term used to cover any form of life, whether animal, plant or microbe. 'Genetic engineering' is concerned with deliberately changing the genes of an organism in order to alter one or more of its characteristics. The term 'genetic manipulation' is used elsewhere, sometimes interchangeably with 'genetic engineering' and sometimes with a more restricted meaning. In this Report we use the term 'genetic engineering' except when quoting from other sources.

1.2 Genetic engineering offers the prospect of major improvements in medicine, in industry and in agricultural quality and efficiency. It is also likely to help in dealing with problems of environmental pollution and to lead to new commercial products. The UK is well fitted scientifically to make advances in genetic engineering.

1.3 As in many other fields of technological innovation, potential benefits bring potential risks. The risks that genetic engineering may entail, and the associated ethical considerations, have been debated since the technology came into existence in the early 1970s. There can rarely have been a new technology which has attracted so much intense discussion of its potential risks from such an early point in its development. To some extent this reflects the nature of the science. There is a natural apprehension stemming from the belief that scientists are now manipulating something as fundamental as life itself. The discussion also reflects an awareness that the relationship between living things and their environment is complex and imperfectly understood. Changes to one may have unknown, widespread and lasting effects on the other. Consideration of the environmental implications of releasing GEOs forms the main thrust of this Report.

Scope of this Report

1.4 Genetic engineering raises a wide spectrum of issues. The Commission has been concerned to:

- examine effects on the environment which may arise from the release of GEOs;
- discuss the risks associated with such releases; and
- consider the procedures necessary to identify, assess and minimise the risks.

In doing so we have considered both the national and international dimensions of the problem and the legal implications. The study has been confined mainly to issues relating to the planned release of GEOs but we also address the question of accidental escape from contained laboratory or factory facilities.

1.5 Medical applications are at the forefront of many of the current developments in genetic engineering. Examples from this field are therefore used where appropriate even though medical and veterinary issues in general are outside our remit.

1.6 The technology of genetic engineering raises ethical, social and political issues such as animal welfare, the possible loss of genetic diversity through the promotion of fewer crop varieties and the possibilities of military or terrorist use. These are touched upon very briefly in this Report. Other important issues, however, such as human gene therapy, human embryo research and the fundamental question of whether mankind should seek to create new forms of life, fall outside our remit as a Commission on environmental pollution and are not considered.

International interest

1.7 Many countries are examining the impact that genetic engineering may have on their commercial future, environmental well-being and society. The European Community and the Organisation for Economic Co-operation and Development are developing legislation and guidelines for their member states in an attempt to achieve consistent approaches. United Nations agencies are involved in promoting the technology of genetic engineering and the assessment of its safety.

1.8 The interest of governments world-wide reflects concerns about the release of genetically engineered organisms. In the USA action by local and national groups has delayed or prevented some release experiments. Denmark exerts tight statutory controls on releases of GEOs and a report to the West German Parliament has recommended a moratorium on the release of certain genetically engineered micro-organisms. In a number of countries, including the UK, voluntary systems of control directed specifically at the release of GEOs have been introduced to supplement existing product and other controls.

Scale of development

1.9 Although there is no reliable information on the number of releases that may be expected over the next few years, it is clear that the technology has reached a threshold, moving from an experimental stage using contained facilities and limited field trials to the widespread marketing of GEOs as products for general use. The addition of commercial pressures to the quest for scientific knowledge makes it even more important to develop a system by which the environmental risks arising from genetic engineering are evaluated, regulated and minimised. Whilst the technology is comparatively accessible and low cost, the evaluation of risks from a proposed release may be lengthy and expensive.

Proposals for regulation

1.10 Against this background, we have drawn up proposals to protect the environment from the risks arising from the planned release of genetically engineered organisms within a framework of statutory regulation. We also make proposals for allowing the maximum disclosure of information to the public and for minimising the risk of damage from the accidental release of GEOs. In doing so we have noted developments internationally, especially in Europe. We have sought to build on the careful work being done by the Advisory Committee on Genetic Manipulation (ACGM), in particular by its

Intentional Introduction Sub-Committee, under the auspices of the Health and Safety Commission (HSC).

1.11 We consider it essential that the release of genetically engineered organisms is conducted from the outset under appropriate statutory control. Regulatory provisions must be capable of development to reflect increases in knowledge. In what follows we recommend a framework within which such provisions may be developed.

CHAPTER 2

THE CONTEXT AND APPLICATION OF GENETIC ENGINEERING

Evolution

2.1 Life is generally thought to have first evolved on Earth some 3–4,000 million years ago. Mankind shares the planet with possibly ten million or more species of plants and animals. Millions of species have evolved, lived and become extinct over this vast time span.

2.2 The basic mechanism driving evolution was proposed by Charles Darwin, over 100 years ago, in 'The Origin of Species by Means of Natural Selection'([1]). There are three main elements. First, many more individuals of a species are born than can possibly survive to maturity. Secondly, individuals are not identical and most of the differences between the variants are genetically determined, that is they are inherited. (We now know that inherited differences arise by mutation and recombination of genes.) Finally, success in the struggle to survive is not randomly distributed across individuals; some variants are more likely to survive than others. This differential survival Darwin referred to as 'natural selection'. The end result over many generations is change (evolution) in the form and function of living things.

2.3 According to Darwin's theory, the evolution of new species takes place very slowly, over hundreds or even thousands of generations, as small differences appear from one generation to the next in diverging populations. When the differences established in diverging populations become such that they will no longer interbreed freely under natural conditions, then the two populations are classified as separate species.

2.4 The full picture is somewhat more complex than the above brief description suggests. For example, *Spartina townsendii* is a salt marsh grass that has invaded large areas of intertidal mudflats in Britain. This new species evolved apparently instantaneously as a hybrid between a native *Spartina* and an introduced American relative and cannot breed with either parent([2]).

2.5 Other aspects of the simple Darwinian model are also the subject of debate. For example, some specialists have suggested that the fossil record sometimes indicates long periods with little detectable change in species composition followed by periods of very rapid change (so-called 'punctuated equilibria')([3]). Others dispute this interpretation. Whatever the precise nature of the mechanisms of evolution, and there are other possible ones not mentioned above, changes in the genetic composition of populations occur from generation to generation. These may be the result of mutations or the result of new combinations of genes created by fertilisation of eggs, pollen transfer or other DNA exchanges. The myriad of new genetic combinations thus produced in each generation is 'tested out' in the environment. Over a period of time, which may be very long, new species develop and other species die out.

Breeding techniques

2.6 For centuries, breeders have been selectively crossing plants and crossing animals in the search for new strains. Increasing sophistication of techniques has enabled plant and animal breeders to make major advances in

disease resistance, yield, quality and many other economically desirable attributes of crops and in the appearance, physiology and other characteristics of animals. Examples of the variation achieved by traditional breeding programmes include the cabbage, cauliflower, Brussels sprout and broccoli, which are all selected variants of the same species (Plate 1), and great danes, corgis and pekineses.

2.7 Commercial breeding techniques are becoming more sophisticated and often take place in specially equipped laboratories. In essence, however, they rely on natural processes of reproduction. Their purpose is to produce varieties beneficial to man but which have failed to occur by chance or, if they have occurred, have failed to become established naturally because they offered no natural advantage to the species. Indeed, they may be viable only with continued human intervention.

2.8 Relying on the artificial selection of single plants with desired characteristics and their intensive propagation, breeding techniques generally allow new, improved strains to be developed and multiplied in a minute fraction of the timescale of natural evolution. The resulting new varieties differ only in degree, however, from the strains from which they were developed. In general the selection and refinement of particular traits in this way is not considered an environmentally damaging activity. It has, however, indisputably changed our environment with the appearance of the countryside reflecting farming practices based on modern breeds and plant varieties. In addition, some crop varieties are dependent on artificial support, such as irrigation, heavy doses of fertilisers or pesticides to produce optimal yields. These factors too have an impact on the environment.

What is different about genetic engineering?

2.9 The techniques of traditional plant and animal breeding have been improved over the centuries but are still restricted, for the most part, to combining different strains or varieties of the same genus. Over the past 40 years key developments in the understanding of genetic structure and its manipulation have opened up new possibilities for engineering genetic changes in ways that had not previously been possible. The box on pages 6 and 7 identifies some of the key events which led to the development of genetic engineering.

2.10 The elucidation of the DNA double helix by Crick and Watson in 1953 was followed by the discovery in the 1970s that the threads of DNA could be cut at specific sites into segments. In 1972 it was shown that such a segment could be 'stitched' end-to-end to any other segment of DNA which had been similarly cut. This paved the way for techniques to remove a specific gene from an organism and either to reinsert it in a different position in the same organism or to move it to a totally different organism where, in either case, it could replicate and function under appropriate conditions. In this way the traits of one organism could be expressed in an unrelated one in a way that could not be achieved by traditional breeding methods alone. The technology of this is described in Chapter 3.

2.11 Organisms derived by genetic engineering can contain genetic information and exhibit properties that have evolved in the context of an unrelated species. These organisms may be produced in days or weeks, rather than the years required for traditional breeding techniques or the millennia for evolution. They are products of the laboratory and may well contain combinations of genes that are extremely unlikely to have occurred in nature in situations where the organisms in question could multiply.

SOME KEY EVENTS WHICH LED TO THE DEVELOPMENT OF GENETIC ENGINEERING	
1860	The principle of cell division to produce new cells in plants and animals is discovered.
1860s	Gregor Mendel's experiments with peas point to the phenomena of dominance and recessiveness of inherited traits.
1869	Frederick Miescher isolates nuclein — known as DNA.
1870s	Herman Fol, Oskar Hertwig, and Edouard Van Bereden detail sexual fertilisation.
1878–1881	Walter Flemming and E. Zacharia identify chromosomes in the nucleus of cells.
1900	All the bases in DNA have been isolated and identified. DNA has been extracted from calf thymus and RNA found in yeast.
1930s	Hans J Muller examines mutation in *Drosophila* fruit flies.
1935	Pat Levene elucidates the structure of the building blocks from which DNA is formed and how they are assembled.
1940	Archibald Garrod, George Beadle and Edward Tatum deduce the one gene — one enzyme relationship.
1940s	Animal cell tissue culture is developed.
1943	Oswald T Avery, Maclyn McCarty and Colin M MacLeod propose the Transforming Principle, that DNA is an information code of life.
1940s	Linus Pauling and Robert Corey suggest that proteins have a helical structure.
1950	Harold C Urey and Stanley L Miller perform simulations of conditions that may have existed early in the life of the earth, to produce simple molecules that are believed to be essential to life as we know it, using mixtures of ammonia, methane and water and electric sparks.
1950–53	Erwin Chargaff identifies the rules relating bases in DNA, that there is the some number of adenines as thymines and of cytosines as guanines.
1951–53	James Watson and Francis Crick deduce the double helix structure of DNA from X-ray crystallography by Rosalind Franklin and Maurice Wilkins.

SOME KEY EVENTS WHICH LED TO THE DEVELOPMENT OF GENETIC ENGINEERING	
1952	Martha Chase and Alfred Hersley show by work on viruses that the genetic information is contained in the DNA and not in proteins.
1953	Fred Sanger and Co-workers complete the determination of the amino acid sequence of the hormone insulin.
1960	Arthur Pardee, Francois Jacob, Jacques Monod, Sydney Brenner and Francis Crick identify the role of messenger RNA in the expression of proteins.
1960s	Severo Ochoa, Marshall Nirenberg and Phil Leder show that RNA codons of the genetic code are universal in almost every cell.
1960–65	The laboratories of Marshal Nirenberg, G. Khorana and Severo Ochoa identify the genetic code words for the amino acids.
1965	Fred Sanger, Walter Gilbert and Alan Maxam devise methods for sequencing DNA and RNA.
1958–65	Francois Jacob and Jacques Monod postulate the structure of the bacterial regulatory gene.
1970	Ham Smith and others isolate and identify the function of restriction enzymes.
1972	Janet Mertz and Ronald Pavis show that restriction enzymes produce DNA fragments whose ends can join together again. Peter Lobbam and Dale Kaiser develop a general method for joining together any two DNA molecules.
1975	Monoclonal antibodies are produced.
1977	The first human gene is cloned.
1982	Genetically engineered insulin is approved for use by diabetics in the USA and UK.
1987	The first genetically engineered micro-organisms are released to the environment in field trials.

Sources:

I Rosenfield, E Ziff, B Van Loon (1984). 'DNA for Beginners'. Writers and Readers Publishing, Inc.

D Freifelder (1983). 'Molecular Biology – A Comprehensive Introduction to Prokaryotes and Eukaryotes'. Jones and Bartlett Publishers, Inc, Boston, USA.

Definition of genetic engineering

2.12 Paragraph 1.1 explains that genetic engineering is concerned with deliberately changing the genes of an organism in order to alter one or more of its characteristics. Traditional plant and animal breeding techniques (paragraphs 2.6–2.8) have a similar purpose and progress in these techniques has produced a grey area of overlap between them and genetic engineering. For this reason, and also because of rapid development in the science of genetic engineering itself, it is not easy to arrive at a precise definition of genetic engineering.

2.13 The essential feature is the concept of the deliberate 'engineering' of an organism's nucleic acid. This may involve the insertion of genes from other organisms, the rearrangement or duplication of genes, the deletion of genes or the construction of novel genes. Techniques which come within this concept of genetic engineering include recombinant DNA (rDNA) techniques (paragraphs 3.10–3.16), micro-injection (paragraph 3.16) and protoplast fusion (paragraph 3.17).

2.14 Protoplast fusion is a technique which is being taken up by traditional plant breeders. When organisms within the same species are involved (intraspecies fusion) it can produce results which previously required many generations of systematic crossing. It can also, however, be used to produce crosses between different species (interspecies fusion) which could not be achieved by more conventional techniques. We consider that the use of protoplast fusion by traditional plant breeders is not in itself sufficient cause for excluding it from the coverage of our definition.

2.15 The box on page 9 contains 5 different definitions related to genetic engineering. The draft definitions prepared by the European Commission and the Health and Safety Executive (definitions 3 and 4) come closest to our view of the appropriate coverage. Our reservations about them concern their restriction to combinations of heritable material which do not occur naturally in the cell or organism in question. This introduces scope for argument about what could or could not occur naturally. In our view, whether a process is considered to be genetic engineering depends on the technique involved and not on whether the outcome might have occurred naturally and an organism should not be excluded from consideration simply on those grounds. This is of particular relevance in the case of gene deletions, which are common events in nature. Our reasons for this are explained in paragraph 5.17.

2.16 It is important that any definition should be kept under review by experts and amended as necessary both to clarify if necessary the position of new techniques and to modify the coverage in the light of experience.

Definition of release

2.17 We adopt the Health and Safety Commission's definition of a deliberate release to the environment, namely use 'without provision for containment such as special procedures, equipment and installations or facilities that provide physical barriers to minimise the organism's spread (and that of its nucleic acid) to the environment'([7]). This definition recognises that no system can ensure complete containment and enables a degree of judgment to be used on what constitutes a release. For example, a genetically engineered sheep in a field might not be considered as released, if the field were adequately fenced to contain it, whereas a genetically engineered micro-organism in the same field would be considered as released since field fences are not adequate to contain micro-organisms.

DEFINITIONS

1. United Kingdom — Health and Safety (Genetic Manipulation) Regulations, 1978([4]).

'Genetic manipulation means the formation of new combinations of heritable material by the insertion of nucleic acid molecules, produced by whatever means outside the cell, into any virus, bacterial plasmid, or other vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation.'

2. United States — Guidelines for Research Involving Recombinant DNA Molecules, June 1983([78]).

'In the context of these Guidelines, recombinant DNA molecules are defined as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described in (i) above. NOTE: Synthetic DNA segments likely to yield a potentially harmful polynucleotide or polypeptide (e.g. a toxin or a pharmacologically active agent) shall be considered as equivalent to their natural DNA counterpart. If the synthetic DNA segment is not expressed *in vivo* as a biologically active polynucleotide or polypeptide product, it is exempt from the Guidelines.'

3. European Commission: Draft Council Directive on the deliberate release to the environment of genetically modified organisms, March 1988([6]).

'Genetically modified organism is an organism (including multicellular and unicellular organisms and subcellular entities capable of replication) in which the genetic material is altered in a way that passes the natural barriers of mating and recombination. Annex 1 indicates the techniques by which such genetic alterations can be obtained.'

Annex 1 contains a list of techniques including recombinant DNA and micro-injection.

4. United Kingdom — Proposed Genetic Manipulation Regulations, 1989([7]).

'Genetic manipulation means the propagation of combinations of heritable material by the insertion of this material, prepared by whatever means outside a cell or organism, into a cell or organism in which it does not occur naturally, either-

a. directly; or

b. into a virus, microbial plasmid or other vector system which can then be incorporated in the cell or organism.'

'Organism means any biological entity capable of replication (whether microscopic or not).'

For the purposes of release to the environment, the Regulations in addition cover 'any live cell or organism which was produced or modified by genetic manipulation, *in vitro* cell fusion or other *in vitro* technique, to form combinations of heritable material which do not occur naturally in that cell or organism.

5. United States — US Congress Office of Technology Assessment, 1988([8])

'In this study, the term 'genetically engineered organism' is used most often to mean an organism to which genetic material has been added or deleted via recombinant DNA techniques. This usage is not, however, absolute, since some regulatory agencies (eg EPA) presently define the term more broadly. Some of the genetic or ecological issues discussed in the study might also apply to organisms produced by means not involving recombinant DNA in the strict sense, such as cell fusion.'

Biotechnology and genetic engineering

2.18 Genetic engineering at present represents a small proportion of all the activities classed as biotechnology.* Biotechnology is defined as the application of scientific and engineering principles to the processing of materials by biological agents to produce goods and services[10]. Cheese making and brewing are early examples.

2.19 Modern biotechnology consists of activities which involve the use of genetic engineering techniques and others which do not. In some activities, living organisms are used in a contained system, whether a vinegar factory or a high containment research laboratory; in others, organisms are deliberately released, or used, in the environment. Examples are shown schematically below.

Organism	Contained systems	Open environment
Engineered	Production of blood anticoagulants by yeast in a fermenter	Spraying 'ice-minus' bacteria onto plants (paragraph 4.8) to prevent frost damage
Non-engineered	Production of vinegar	Introduction of Myxoma virus to UK to control rabbit population

2.20 There have of course been many releases of plants and animals which are the product of the traditional breeding techniques discussed above. Exotic parasites and predators have also been released since the mid-19th century to control plant pests; the introduction of the Australian *Vedalia* beetle, a ladybird, in California, for example, served to control certain citrus pests. Insects, mites and fish have been used as biological herbicides[38]. Conventionally selected micro-organisms have also been released to the environment. The nitrogen-fixing bacterium *Rhizobium* has been used extensively in enhancing the cultivation of nitrogen-fixing plants in many parts of the world (Plate 2) for almost a century[92]. In many countries the seeds of nitrogen-fixing plants are coated with a solution containing *Rhizobium* before planting. Strains of the bacterium *Bacillus thuringiensis* (Bt) have been used as a commercial pesticide in agriculture and forestry for more than 20 years[107], and at least 20 pesticide preparations based on naturally occurring viruses are commercially available[38].

2.21 The commercial use of genetically engineered organisms has so far been exclusively in contained systems, most of them in medicine, for example in the production of human insulin by bacteria or yeast[9] or in the manufacture of diagnostic kits[16,17]. Deliberate releases are so far experimental. Until the beginning of 1988 there had been about 30 such releases worldwide. During 1988, however, there was a dramatic increase in the number of experimental trials involving plants and by the end of the year about 80 experimental releases had taken place. In the UK there have been 6

* The word 'biotechnology' was used, and the importance of the activities it refers to was recognised, more than 50 years ago. Sir Julian Huxley, introducing a lecture to be given by Professor L Hogben, said, 'the machinery and the technology at present in use are for the most part crude and primitive compared with what might be achieved; biology is as important as the sciences of lifeless matter; and biotechnology will in the long run be more important than mechanical and chemical engineering.' (The Retreat from Reason, Hogben L, published by Watts and Co, 1936.)

experiments which have been treated as releases, all involving organisms of potential use in agriculture or forestry. The first commercial products may soon become available and may include herbicide resistant and pest resistant plants.

2.22 The total value of world sales in 1987 of genetic engineering products has been estimated at some £400 million per year, of which nearly half is accounted for by diagnostic kits and the remainder by a small number of drugs and vaccines([11]). Total annual sales of pharmaceuticals, for comparison, are estimated at about £60,000 million, excluding the Eastern bloc([12]). The value of total sales of GEOs and their products is expected to increase rapidly, however, as new seeds, pesticides and herbicides become commercially available. It has been estimated that genetically engineered products could take a substantial share of the £40,000 million world market for seeds and agricultural chemicals([11]). The technology of genetic engineering will make possible an enormous increase in the number of releases, in the diversity of the organisms released and in the scale on which the releases take place.

Potential products from genetic engineering

2.23 In medicine, genetic engineering has been used to develop vaccines, drugs, diagnostic kits and other products. Examples include a genetically engineered vaccine for hepatitis B([13]), diagnostic kits([16,17]) for this and other human diseases and blood anticoagulants([14,15]). Gene therapy, whereby genes are inserted into patients' cells, could result in cures for diseases, such as sickle cell anaemia, which have a genetic origin([18]).

2.24 In agriculture, pest resistant plants are being developed (Plate 8) by inserting into the plants *Bacillus thuringiensis* toxin genes([19]). A different technique is being developed in an attempt to protect lodge pole pine trees against destructive caterpillars([20,21]): a virus is being engineered to attack the caterpillars more effectively than does a naturally occurring virus. Such products could dramatically reduce the use of chemical pesticides and the associated environmental problems. Tomato plants which are resistant to tobacco mosaic([22]) and other viruses are being generated by genetic engineering. By engineering micro-organisms to help plants obtain nutrients from their surroundings, fertiliser use could also be reduced. Plants are being engineered to withstand herbicides so that the herbicides can then be used to control field weeds more effectively without harming the crops ([23,24]). In the area of animal husbandry, improved vaccines for animals([25]) and engineering for disease resistance could reduce disease and the use of veterinary pharmaceuticals.

2.25 In areas other than health care and agriculture, the early commercial uses of genetically engineered organisms are likely to be in food processing([26]). Released organisms are also likely to be used in mining, for the recovery of heavy metals, in the control of oil spills, for water purification and in pollution control generally([27,28]). Naturally occurring micro-organisms are already used for copper extraction, for example, and for degrading chemicals in toxic waste([156]). New organisms may also be used in the longer term to generate alternative sources of fuel replacing conventional ones such as timber or oil([157]) and for the development of 'biosensors' to assist with control of industrial processes or for diagnostic use in medicine([158]).

2.26 The uses mentioned so far are for peaceful purposes. Genetic engineering techniques could also be applied to the production or modification of biological agents for military or terrorist uses. As with non-engineered agents the potential harm from such uses could of course be very great([159]). The

development, production and stockpiling of biological weapons are banned under the 1972 Biological Weapons Convention, to which the UK and 110 other countries are party. The use of biological weapons in war is prohibited under the 1925 Geneva Protocol (which also prohibits the use of chemical weapons). The 1972 Biological Weapons Convention was reinforced in 1986, following a Review Conference, by four voluntary confidence building measures. These include exchanges of information about research on biological materials requiring high containment and about outbreaks of infectious diseases which appear to deviate from normal patterns. A further Review Conference will take place before the end of 1991. It has been suggested to us([34]) that widespread knowledge of the Convention, and a greater openness about advances in biological science, are important in reducing fears that new technologies will be used for non-peaceful purposes.

2.27 The prospects for genetic engineering may be compared to those for the agricultural chemical industry in the early 1950s. The scope of genetic engineering activity is still small but expansion is expected in the near future, with important and unpredictable consequences for economic and social development. As in the 1950s, the characteristics of products — whether chemicals then or organisms now — are better understood than the nature of their impacts on the environments in which they will be used. The opportunity exists to learn from the experiences and the predictions of the past in order to build environmental foresight into any necessary regulation of these new products.

CHAPTER 3

THE TECHNOLOGY OF GENETIC ENGINEERING

Introduction

3.1 Genetic engineering has recently expanded at a speed which is unprecedented in the life sciences. There is thus a plethora of new techniques and terminology. In this chapter some of the basic concepts are outlined and a few examples of the key processes underpinning the technology are described([29]).

3.2 Genetic engineering involves the manipulation of nucleic acid, especially deoxyribonucleic acid (DNA). DNA is present in all living cells and contains the information for cellular structure, organisation and function. Below we consider:

- the biological background in which DNA occurs and functions;
- the structure of the DNA molecule and how it directs the production of proteins;
- examples of techniques which are used in the re-organisation of DNA by genetic engineering; .
- the transfer of DNA to another organism; and
- the conditions necessary for it to function there.

The biological background in which DNA occurs and functions

3.3 Living organisms, from the most complex animal to the simplest microbe, are composed of cells. Organisms such as bacteria and some algae are usually composed of one cell only and are said to be 'unicellular'. Other organisms are 'multicellular' containing many cells, often numbered in millions, which differ in appearance and function, but together contribute to the success of the whole organism.

3.4 DNA contains the information that determines and controls the way cells, and thus organisms, function, grow and divide. Genes (paragraph 3.8) are contained in long molecules of DNA which are linked together in structures within the cell called chromosomes. The simplest organisms have only one chromosome. Many organisms contain more than one chromosome, enclosed within a membrane forming part of the nucleus of the cell, Figure 3.1.

3.5 In addition to chromosomal DNA, some bacteria and fungi possess plasmids, Figure 3.2, which are usually tiny, circular molecules of DNA. These also carry genes. Most bacterial cells have one or more plasmids but some contain none. Where there are several plasmids in a bacterial cell they may be different or be multiple copies of the same plasmid. Some plasmids may transfer readily from one bacterium to a wide range of other bacteria. Other plasmids transfer only between closely related bacteria whilst others apparently do not transfer at all.

The structure of DNA and how it directs the production of proteins

3.6 The structure of the DNA molecule, the famous double helix, consists of two intertwined backbones made by joining together sugar (deoxyribose) and phosphate molecules alternately. Chemicals known as nucleotide bases are

attached, one to each sugar moiety, and link the two chains. There are 4 nucleotide bases: cytosine (C), guanine (G), adenine (A) and thymine (T). They are always arranged along the backbones in such a way as to form two kinds of weakly joined base pairs - cytosine opposite guanine and adenine opposite thymine.

3.7 When cells divide, the two strands of the double helix separate and, because of the invariant pairing of the bases, each strand of DNA acts as a template on which a copy of the other complementary strand is laid down, thus forming two double helices. As a result each new double helix consists of one helix from the original cell and a new complementary helix produced using that original helix as a template, Figure 3.3.

3.8 The genes exercise their control by directing the synthesis of proteins, which are important structural elements of cells and also the catalysts which bring about the biochemical reactions which maintain life. Proteins are long molecules made by joining together amino acids in a particular sequence which is controlled by the order of the nucleotide bases in the genes. A group of three consecutive bases (for instance cytosine, thymine, adenine), called a codon, brings about the addition of one of 20 different amino acids or gives the signal to start or stop the synthesis of a protein. The gene is thus said to code for a particular protein and when producing it is said to express the protein which is known as the gene product. A typical mammalian cell may contain 50,000 to 120,000 genes and as many as 2.5 billion base pairs, while even a virus will contain over 5,000 base pairs.

Examples of genetic engineering

3.9 The purpose of genetic engineering is to introduce, delete, or enhance a particular trait in an organism. This is achieved either by inserting foreign genes (that is, genes from another organism) or by altering the existing genetic make-up of the organism. The following sections describe some of the procedures by which foreign genes are inserted into an organism. In most genetic engineering projects this involves extracting DNA from one organism, manipulating or restructuring it and then transferring it into another organism.

The isolation of genes

3.10 Large pieces of DNA can be extracted from cells and purified without significant damage. As mentioned briefly in paragraph 2.10, the breakthrough in the basic technology underpinning genetic engineering was the discovery of the means by which DNA could be cut up and rejoined precisely. This cutting is done using restriction enzymes. These enzymes were first extracted from bacteria and are named after the bacterium in which they are found. They 'recognise' specific combinations of bases, usually of 4 or 6 base pairs, in the DNA double helix and cut these at specific sites as shown in Table 3.1. Thus the restriction enzyme HaeIII (from the bacterium *Haemophilus aegyptius*) will cut a DNA molecule at every site where the sequence GGCC is present. Similarly BalI (from the bacterium *Brevibacterium albidum)* will cut at every site where the sequence TGGCCA is present.

3.11 Two pieces of DNA can be joined by an enzymatic process called ligation to make a longer double helix. It is becoming increasingly possible to isolate, from the vast array of DNA present in an organism, the DNA fragment carrying the gene coding for a specific protein. While the identification and isolation of genes is still a time-consuming process and often technically difficult, it can be expected that the location and function of tens of thousands of genes will be determined over the next quarter of a century.

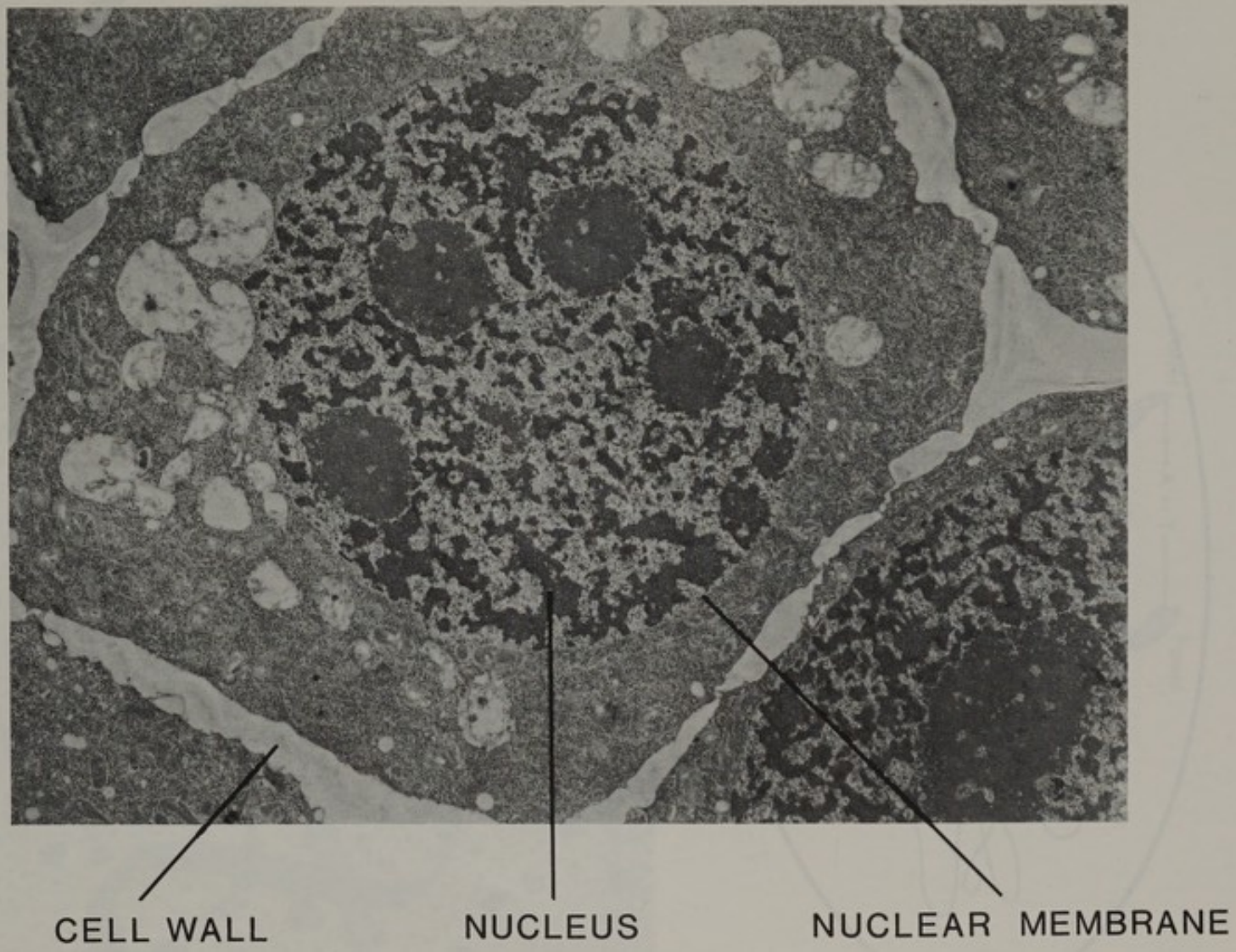
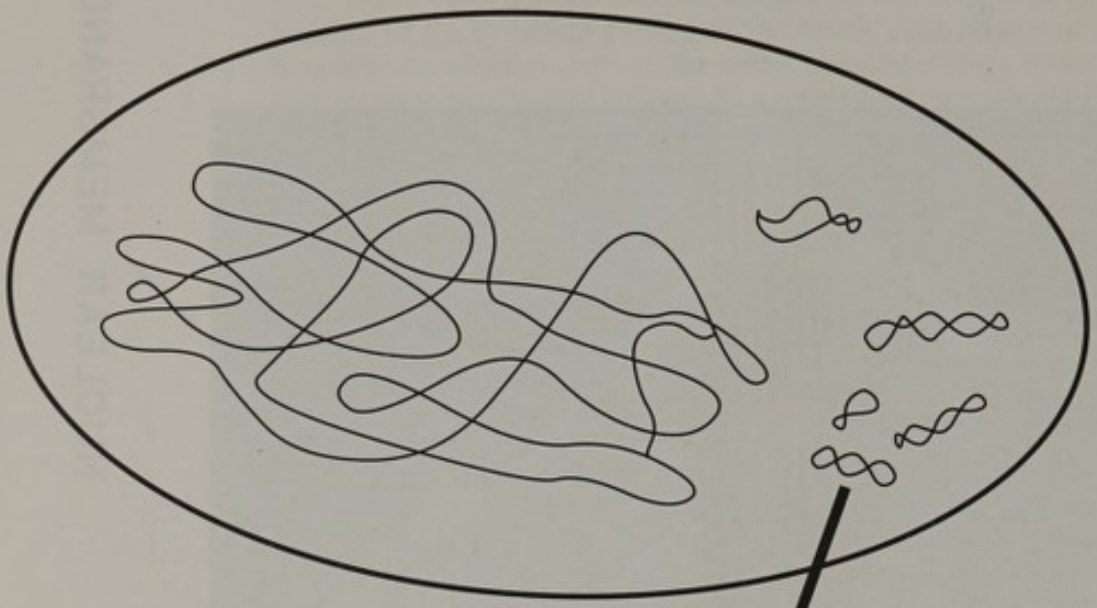
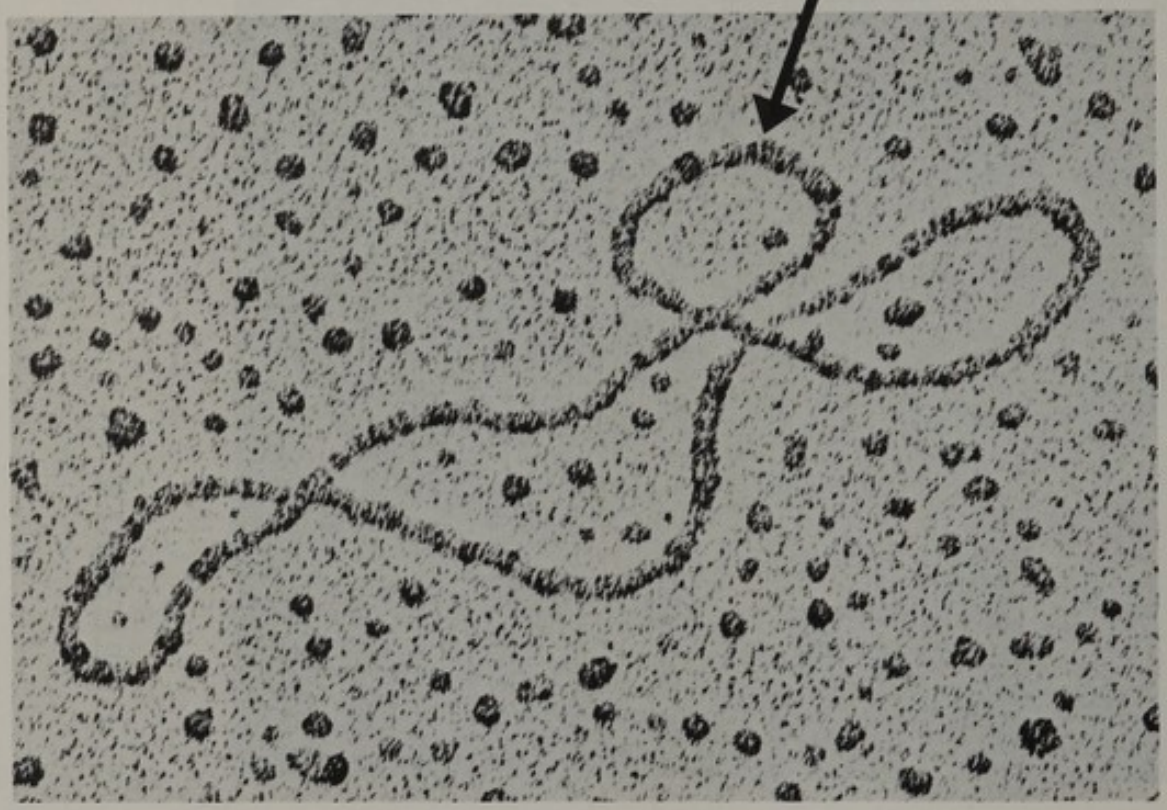


Figure 3.1 A section through a plant cell.



(a)



(b)

Figure 3.2 (a) A bacterium with chromosomal and plasmid DNA. (b) Plasmid photographed through an electron microscope.

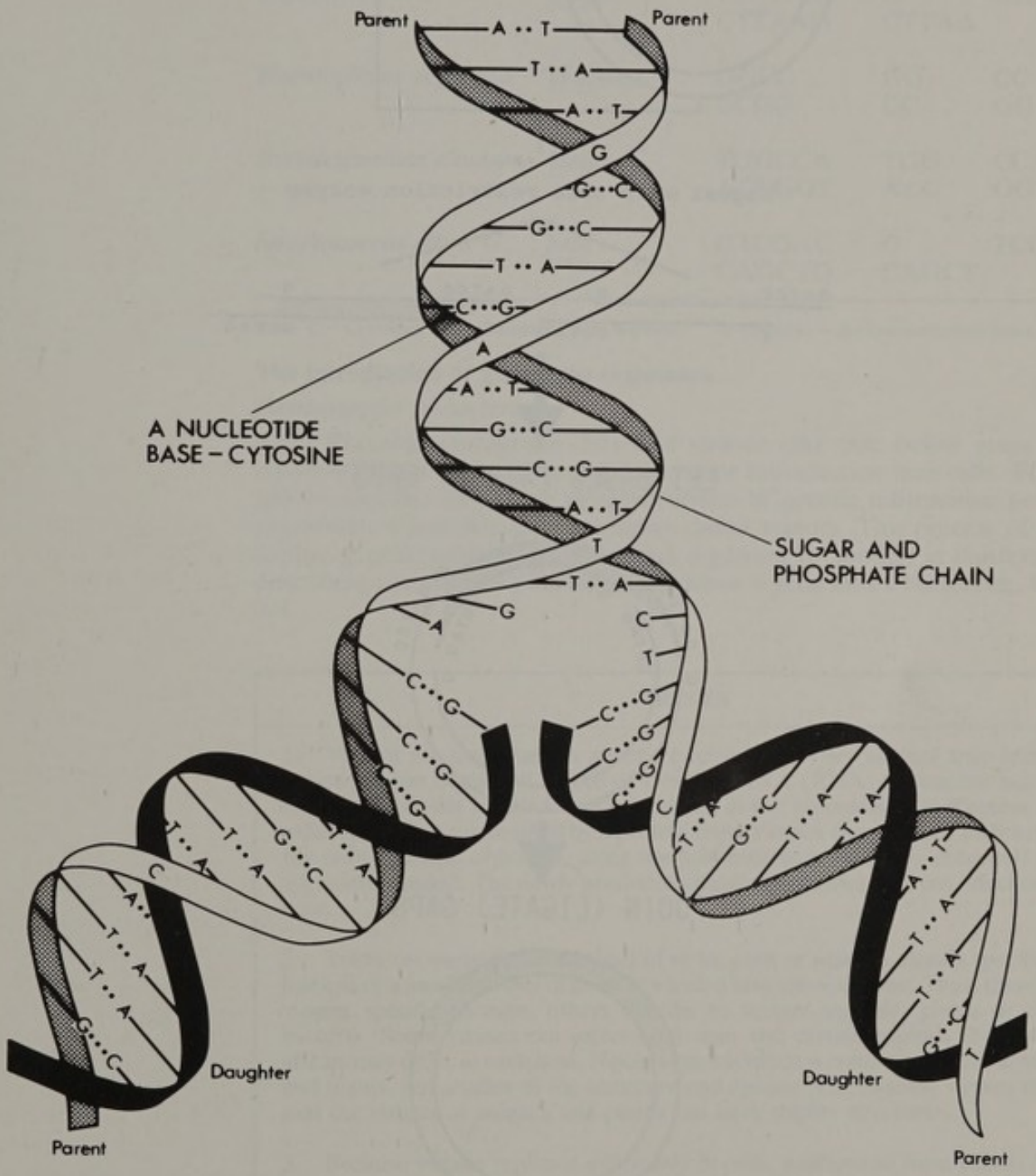


Figure 3.3 The DNA double helix with the parent strand splitting and daughter strands forming.

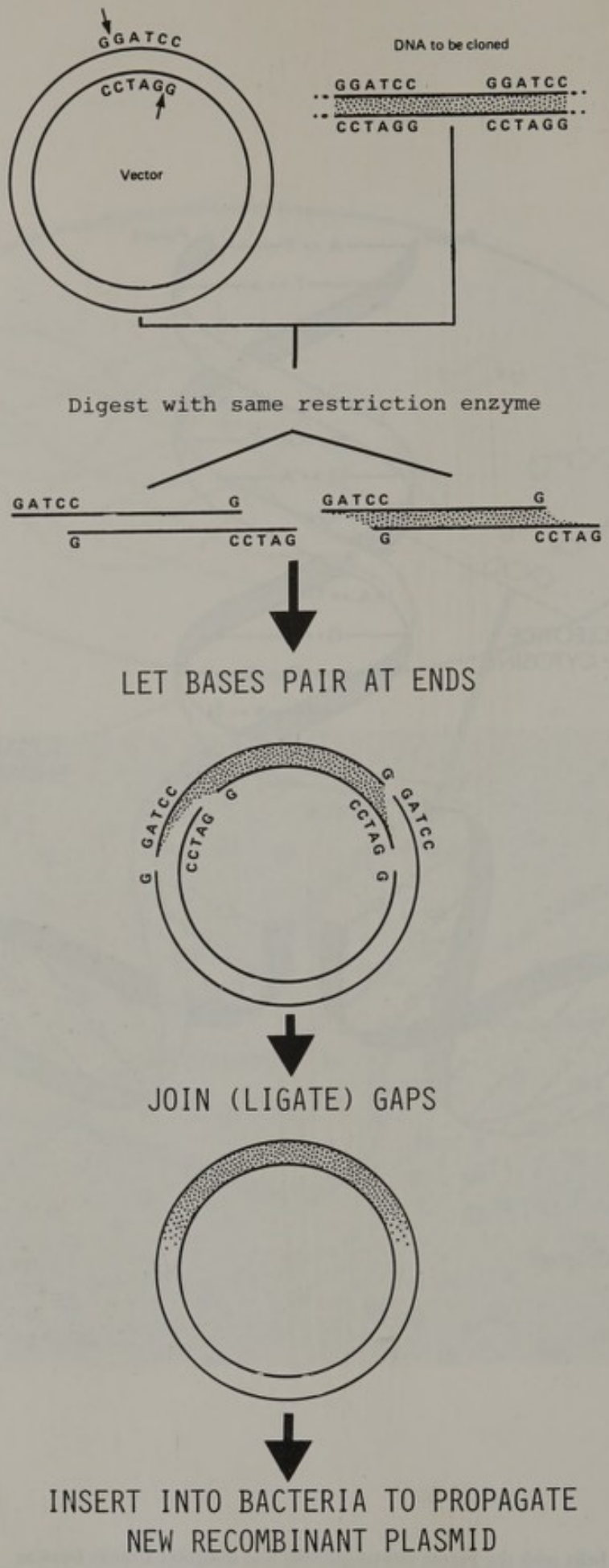


Figure 3.4 The use of a plasmid to introduce a gene into a bacterium.

Table 3.1

Some examples of restriction enzymes showing their cleavage sites

Micro-organism producing the enzyme	Name of enzyme	Cleavage sequence	Sequences after cleavage
Escherichia coli	EcoRI	GAATTC CTTAAG	G AATTC CTTAA G
Haemophilus aegyptius	HaeIII	GGCC CCGG	GG CC CC GG
Brevibacterium albidum	BalI	TGGCCA ACCGGT	TGG CCA ACC GGT
Streptococcus albus G.	SalI	GTCGAC CAGCTG	G TCGAC CAGCT G

Note: C = Cytosine; G = Guanine; A = Adenine; T = Thymine — the four nucleotide bases of DNA

The introduction of genes into organisms

Gene transfer to bacteria

3.12 Plasmids (paragraph 3.5) and viruses (the box below gives more information on viruses) can replicate after introduction into cells. For this reason they are commonly used as carriers of genetic information between organisms, when they are sometimes called vectors. This process of transferring genetic information from one organism to another is illustrated by describing the use of a plasmid to introduce a gene into a bacterium, Figure 3.4.

VIRUSES

1. Viruses are important in genetic engineering. They are not true cellular organisms but consist of a core of DNA or RNA (RNA, ribonucleic acid, is chemically similar to DNA and is involved in the processes of replication and other functions) surrounded by a protein coat. Viruses can replicate only within the cells of a host organism, using the host cells to provide the chemicals and apparatus needed. The newly produced viruses escape and then can infect other cells.

2. There are many different kinds of virus, each of which is usually specific to just one or a small number of hosts in which it may cause disease. Thus, there are viruses specific to man, others specific to certain animals, plants or even bacteria. Some viruses can infect both man and certain animals though the effects may differ in each host. None is known which is common to both animals and plants, but studies of the structure and nucleic acid of some viruses show that the viruses of animals and plants can have similar structures.

3. Because viruses replicate efficiently in cells, and spread from cell to cell, they are used for the introduction of foreign genes into animal or plant cells. The new gene is inserted into the viral genome in addition to existing genes or in place of a non-essential gene.

4. Appendix 4 gives more information on viruses.

3.13 It is usually possible to choose a specific restriction enzyme to cleave the plasmid open at one site only. A piece of DNA carrying one or more of the

genes which it is desired to transfer can then be inserted into the gap. This plasmid now contains the genes of two organisms and is thus known as a hybrid or recombinant plasmid. It can then be transferred into its new bacterial host. To do this, it is necessary to mix the plasmids and the recipient bacterium together in a solution which makes holes in the cell membrane of the bacterium to allow the plasmid to enter. The plasmid usually contains a 'marker gene' of some sort to enable the scientist to check that it (and thus its inserted gene) are inherited in the recipient cell. Antibiotic resistance genes are often used as markers; only cells which have received the plasmid, and in which it replicates, will then grow when the bacteria are incubated in a culture medium containing the relevant antibiotic. Replication of the bacterial cells, containing in this case the recombinant plasmid, produces identical copies of the introduced DNA, a process known as cloning.

3.14 It is possible to synthesise chains of nucleotides (that is, to make artifical DNA) in the laboratory and to insert them into a vector. The technique is being used to make very specific alterations to the DNA; for example, chemically synthesised DNA may be made which has only a single base pair change from the native DNA. This may result in a single amino acid change in the protein which may then function differently. Larger, more complex substitutions and changes can also be made.

The transfer of viral DNA into yeast

3.15 The transfer of viral genes into yeast cells illustrates not only the possibility of gene transfer between organisms other than bacteria but also that genetic engineering can bring about important results beneficial to man. A vaccine for hepatitis B has been produced by genetic engineering([13]). DNA from the virus causing this disease was cloned in the bacterium *Escherichia coli* and the small fragment of viral DNA coding for a protein antigen on the surface of the virus was identified. This surface antigen can activate the human immune system. The small DNA fragment was then purified, concentrated and integrated into another plasmid which had the capacity to replicate in yeast and to generate its gene product there. The new plasmid was transferred into yeast and cells making the product were propagated in large fermenters. From the mass of yeast cells produced, the Hepatitis B antigen was isolated and purified to generate a successful vaccine. It has satisfied stringent safety tests and is now in wide use.

Gene transfer to higher plants

3.16 Several methods of introducing DNA into plant cells are in common use. For some species it is possible to introduce the DNA into protoplasts (plant cells which have had their walls removed) in much the same way as for bacteria. It is also possible to inject DNA from a very small syringe into the cell or its nucleus (micro-injection). Another method is to coat minute particles with DNA and then to fire them into the cell. The commonest method at present for gene transfer into plants is founded on the natural gene transfer process evolved by a bacterium, *Agrobacterium tumefaciens*. This naturally occurring soil bacterium transfers a specific segment of a plasmid into plant cells. Once plant cells have received the DNA, and it has been inserted into their chromosomes, the cells can be grown to produce normal whole plants.

3.17 Protoplast fusion is another way in which plants can be genetically manipulated. The walls of cells of two plant species are removed and the two protoplasts which remain are encouraged to fuse to produce a hybrid cell (Plate 3) from which new plants can be regenerated. One of the very first experiments of this type was to fuse tomato and potato protoplasts. The fused

cells were incubated in complex culture media where they produced first tissue cultures and eventually whole plants. In other experiments the protoplasts of a cultivated potato have been fused with those of a wild potato, *Solanum brevidens*, which is resistant to potato leaf roll virus (the cause of a major disease of potatoes), the intention being to produce commercial varieties with resistance to this disease([30]).

Gene transfer to animals

3.18 Animal genes can be isolated and manipulated just as plant genes can. For example, animal genes have been inserted into bacterial plasmids and then into bacteria. It is also possible to insert foreign genes by micro-injection into developing animal embryos to produce transgenic animals (Plate 4). Transgenic mice, sheep and cows can be generated in this way and will express the foreign gene to produce proteins([109]). Such technology is still in its infancy. Two problems at present are that only a small percentage of the genes injected are integrated into the host DNA and, of those that are, only a few function in a predictable way([160]).

Conditions necessary for transferred DNA to function in the recipient organism

3.19 Techniques for producing genetically engineered organisms have developed rapidly over the past 10 years and some products, mainly pharmaceuticals synthesised in bacteria and yeasts, are already on the market. For many of the likely applications, however, a number of technical difficulties still have to be overcome before reliable products become available.

3.20 Although it is possible to transfer genetic material from one organism to another, the result of such a transfer can be difficult to predict. This is because the biology of an organism is determined by the complex interaction of groups of genes which have evolved together.

3.21 Multicellular organisms are made up of cells, tissues and organs which have different functions, such as blood, hair, skin, eyes, liver, muscle, bones and fins. However, every cell of a multicellular organism contains a complete set of chromosomes and genes. Cells of different tissues and organs have different properties and functions because the genes which are expressed differ from tissue to tissue and sometimes from cell to cell. The process of cell specialisation is termed differentiation. Special genes called regulatory genes are involved in determining the various patterns of gene expression. When a new gene is inserted into an organism by genetic engineering it is often important that it adopts the correct pattern of expression during tissue and organ differentiation. This is not easy to design; ensuring that genes are appropriately and reliably expressed in a new cellular background is often difficult.

3.22 Changes in the bases in genes can occur naturally and are called mutations. Mutations may be induced by external sources such as ultra-violet or X-ray radiation or certain chemicals, or they may occur spontaneously through errors during the replication of the DNA. Cells have systems that check newly replicated DNA and correct it if copied incorrectly but the systems are imperfect and some errors may persist. The transcription of the DNA to make proteins is also subject to error. Usually such errors are very infrequent, but the frequency can increase when a gene is in a different host. For proteins that have specific functions, such as hormones, small changes in amino acid sequence can have a major effect on their activity. We have received evidence that transcription errors in yeast can be so high that at least half the protein produced from a cloned gene could be defective([77]).

CHAPTER 4

THE ENVIRONMENTAL IMPACT OF RELEASED ORGANISMS

Introduction

4.1 Chapter 2 described examples of potential applications of genetic engineering in many areas of activity including improved health care, agriculture and pollution control. As with many new technologies, the potential for improvement is accompanied by a risk of undesirable effects. A major difference between the release of GEOs and the products of other technologies is that, under certain circumstances, GEOs can reproduce, multiply and spread. This chapter illustrates how the release of GEOs might affect the environment. Releases have so far been on an experimental scale and have had no known adverse environmental effects. Some recent releases and the concerns that have been expressed about them are, however, discussed. The chapter also considers how the environment has been affected by the introduction of non-engineered organisms in order to illustrate the impact that organisms in general can have. Chapter 5 then assesses the key issues arising from the release of GEOs to the environment.

4.2 Organisms which survive and become established could affect the environment in a variety of ways — both beneficial and undesirable. Some releases may alter the diversity of species in the environment, including changing the composition of existing communities. Such effects could produce noticeable changes in the countryside, locally or more widely, and could also have an economic impact, for example if the new organisms proved to be successful predators, competitors, parasites or pathogens of crop plants. Some organisms could pose a threat to human health. At the most extreme, new organisms could conceivably affect major environmental processes such as weather patterns, the nitrogen cycle or other regenerative soil processes.

Examples of environmental effects from the release of GEOs

4.3 One of the first releases of a GEO in Great Britain was of a genetically engineered virus as part of a programme aimed at improving biological control of certain caterpillar pests([21]). The unmodified virus attacks only specific caterpillars and has been used safely as a biological insecticide for years but, in comparison with chemical pesticides, it is slow acting. The releases in this programme, described in more detail in Appendix 5 paragraphs 2–17, were carefully assessed to ensure that they posed no unacceptable risks. We nevertheless looked closely during our study at some of the issues that may be raised by the release of genetically engineered viruses. Manipulation of a virus for a particular purpose could alter other characteristics in a harmful and unintended way. It might, for example, unintentionally alter its virulence or widen the range of susceptible organisms. The manipulation of an insect virus is likely to be a potential risk mainly to other insects, though this might include beneficial insects such as pollinators. This specificity cannot, however, be relied upon. Some viruses, such as those causing influenza and rabies, infect a much broader range of species([31,32]). One witness considered that the Hepatitis delta virus, which infects humans, may contain a part of a plant virus which had been 'captured' by a human virus([33]).

4.4 The range of organisms affected by a virus may be altered in less direct ways. For example, a laboratory study of a pathogenic plant virus showed that it was possible, by altering a single gene, to change the range of insects that could carry it[62]. Since certain insects prefer certain plants, this could enable the virus to come into contact with previously unaffected plant species. Other indirect mechanisms which widen the target range may also exist. Viruses are described in more detail in Appendix 4. The issues raised by the genetic manipulation of viruses are discussed further in paragraphs 5.31–5.34.

4.5 Projects intended to engineer plants to produce insect toxins have been referred to in paragraph 2.24. In such cases the possibility that the toxin may appear in a part of the plant that might be eaten by non-target animals or by people must be borne in mind. Many plants grown for human consumption contain toxins, however. For example, some kinds of beans need cooking to make them safe for humans to eat and potatoes and rhubarb are familiar examples of plants of which parts are poisonous whilst other parts can be eaten. It is important to be aware of the existence of these toxins and the preparation necessary to make them safe.

4.6 Another concern with insect resistant plants is that the cultivation of thousands of acres of the crop may encourage the development and spread of insects resistant to the toxin. This possibility would be increased if there were a strong likelihood of the gene which generates the toxin spreading to other plants by conventional means, for example by pollen transfer. Spread of the gene might also result in other, non-target insects falling victim to the toxin.

4.7 The converse of the example mentioned in paragraph 4.5 is that organisms might be engineered to remove or disable genes normally causing toxicity, pathogenicity or virulence, so that they could then be used in circumstances in which they would otherwise be undesirable. In such cases concern will focus on the possibility that these harmful genes may be unexpectedly reacquired or reactivated, perhaps under environmental conditions unlikely to occur during testing in the laboratory.

4.8 Different issues were raised by the release of 'ice-minus' bacteria in the USA, described in Appendix 5 paragraphs 18 and 19. These genetically engineered micro-organisms were sprayed experimentally onto strawberries and potatoes in California to compete with micro-organisms that induce ice formation and so to prevent frost damage. There was some concern that, if the use of such GEOs eventually became so widespread that they became prevalent in the atmosphere, their action might also lead to changes in local climate by preventing the formation of rain droplets. Following two studies commissioned by the US Congress Office of Technology Assessment (OTA) it was concluded that the likelihood of climatic change was negligible even in the event of large-scale agricultural use of this GEO[8]. The example nevertheless emphasises the need for care to be taken about possible environmental consequences.

4.9 A number of elements, including nitrogen, are essential for life. The amounts that are biologically available can control the number of living organisms an environment can sustain. Some genetic engineering research is trying to produce plants and animals which use these essential elements more efficiently. For example, bacteria such as *Rhizobium* are being manipulated to enhance nitrogen fixation in the soil. Again the OTA commissioned a study of this work to investigate whether there might be any consequences for the nitrogen cycle. Their conclusion was that the probability of adverse consequences was very remote and that genetically engineered *Rhizobium* could be safely used in field tests to investigate the consequences of their release. They

also remarked that normal crop rotation could produce greater changes than microbial inoculations to the patterns of nitrogen distribution and movement in an ecosystem([8]).

4.10 Several herbicide manufacturers are developing crops containing genes which confer resistance to specific herbicides. This raises two issues. First, the herbicide resistant genes might spread, for example in pollen, to weeds which would then also become resistant to the herbicide([8,88]). The risk might be greater if the crop were related to a weed, for example as rape is related to wild mustard. Secondly, there is concern that the engineering of plants resistant to herbicides could lead to the greater use of herbicides which could, under some circumstances, be environmentally damaging. On the other hand, the outcome might be environmentally advantageous if farmers were able to replace an environmentally harmful herbicide by a less harmful one or to control weeds using lower quantities of herbicide. These possibilities illustrate some of the wider, less direct repercussions that might arise from the use of new organisms.

4.11 Another possible indirect effect arises from the practice of inserting into genetically engineered micro-organisms genes which confer resistance to certain antibiotics. This is a useful and fairly common technique (paragraph 3.13) but it has to be considered against a background of increasing concern about the spread of antibiotic resistance in the environment([8]). It would be highly undesirable if the release of a GEO accelerated the dissemination of antibiotic resistance genes in pathogens, particularly if the antibiotics concerned were used for human or animal therapy.

4.12 The preceding paragraphs have illustrated some of the environmental concerns, mainly conjectural, that have been raised about the release of some GEOs which are currently the subject of research. We propose in later chapters arrangements which we consider will enable these concerns, and others discussed in Chapter 5, to be effectively addressed.

Environmental impact of non-engineered organisms

4.13 In view of the limited experience of the release of GEOs to the environment we have found it helpful to study some of the environmental effects which have resulted from releases of non-engineered organisms. Although they do not necessarily provide an exact analogy for releases of GEOs, study of their effects helps in understanding and anticipating the potential impact of GEOs on the environment.

Exotics

4.14 An exotic is an organism transferred from its native habitat into one in which it is not normally found. The term 'exotic' can be applied to plants, animals and even micro-organisms. There is considerable experience of the introduction of exotics into new environments. It has been argued that the analogy between the introduction of exotics and the release of GEOs is limited([8,35]) because exotics are already genetically well-adapted, through years of natural selection, to their native habitat where their proliferation is held in balance by a variety of ecological factors. In a new environment the exotic has the opportunity to proliferate if the various balancing factors of the native habitat are missing. In contrast, although the release of a GEO may sometimes be to a foreign environment, on other occasions it may only involve the reintroduction into its native habitat of an organism containing just one or a few genetic modifications.

4.15 If a genetically engineered organism were released into an environment in which the unmodified organism was not native, experience with exotics could be highly relevant. Even if the release were into the native environment, the unmodified organism might be well adapted through natural selection to survive in that environment and the genetic manipulation might, possibly deliberately, upset the ecological balance that normally helped to limit the population growth of the unmodified organism.

4.16 There are many well-researched cases of the environmental impact of exotics. The box on pages 22 and 23 summarises some conclusions from a recent review of the literature[36]. The following paragraphs illustrate a few cases.

4.17 An example of a controversial exotic which has altered the landscape is the spread of *Rhododendron ponticum* in woodlands and on heaths in the UK (Plate 5), threatening many native species and bringing about a loss of diversity of native plants and animals[37]. Some people, however, view it as an attractive addition to the British countryside.

4.18 Another example is Dutch elm disease. The introduction of a particularly virulent strain of this fungus, probably from America, has progressively killed most of the UK's large elm trees (*Ulmus* species). The loss of these elms has markedly affected the appearance of much of the British landscape (Plate 6). Other environmental effects resulting from the loss of elm trees are discussed in the box on page 24. Many of the examples mentioned later in this chapter have also had major impacts on the landscape.

4.19 A third example is the introduction in 1960 of the Nile perch, *Lates niloticus*, into Lake Victoria, Africa, which caused a series of far-reaching environmental and economic effects[39]. The perch was introduced to improve the fisheries and as a sport fish to encourage tourism. It is, however, a predator of the native fish which have as a result become very scarce. In addition, the native fish could be dried in the sun for long term storage and consumption, while the introduced perch cannot be so preserved because it is oily and requires cooking. Cooking the perch has led to deforestation of several of the Lake's islands and parts of the shore to provide fuel. It is predicted that eventually the loss of the native fish from the lake will lead to a collapse in turn of the Nile perch population, leaving few fish in the lake, destroying the fishing industry and resulting in the loss of a major source of food for local residents.

4.20 When *Pinus cembra*, a two-needle European pine, was introduced to the UK in about 1900 it probably brought with it an Asian pathogen, a pine blister rust, *Cronartium ribicola*[40]. The rust needs as part of its life cycle a pine and a species of *Ribes*, for example the blackcurrant, *Ribes nigrum*. Five-needle pines such as the Weymouth pine (*Pinus strobus*) are very susceptible to the rust so that it is now almost impossible to grow five-needle pines in the UK. In America, where *Pinus strobus* is grown despite the rust for the excellence of its timber[41], currants and gooseberries are removed from within a quarter of a mile of the pine trees to control the spread of the rust[42,43].

4.21 Although exotics can become pests, their effects vary in severity. In parts of Australia introduced rabbits have done major damage. In Britain rabbits are not native animals and they are certainly agricultural pests, but rabbit grazing was an important factor in maintaining some of Britain's most interesting and varied plant communities on chalk downlands and on the Breckland heaths. The loss of rabbits from these systems due to the introduction of another alien organism, Myxoma virus, presents a threat to the existence of the typical heath and downland flora as denser herbaceous

INTRODUCTION OF EXOTIC ANIMALS AND BIRDS AND THE EFFECTS ON THE INDIGENOUS ECOLOGY

1. There have been many attempts to evaluate the effects of the introduction of exotic plants and animals on the indigenous ecology. This is, however, difficult to do for a number of reasons, some of which are listed below:

- Most introductions are failures and are, therefore, often not recorded.

- The effects of few introductions have been properly studied.

- It is often difficult to be sure that an ecological effect has occurred or that it was directly or indirectly caused by the introduced exotic.

- There is a strong bias towards recording introductions that have caused a decline in, or extinction of, a native species.

- Certain geographical areas, particularly oceanic islands, have been intensively studied for the effects of exotics, whilst other areas have been ignored.

- There has been a tendency to study the effect of introducing larger animals and plants and the effects on larger animals and plants of introductions. Consequently, little is known about the effects of introduced insects or micro-organisms, except where they have caused diseases, or effects on indigenous insects or micro-organisms by introduced exotics.

2. The following summarises the results of one recently published paper([36]) on the effects of introduced exotics which became established, to indicate the significance of the problem worldwide. The paper was based on a review of some 400 published papers. It records 788 introductions of 118 types of mammal, of which 363 introductions were of 69 types of herbivore, 307 of 36 omnivores, and 118 of 13 strict predators. The 10 most commonly introduced types included the common rabbit, brown and black rat and the domesticated cat, dog and goat; these accounted for about 54% of the introductions. There were 771 introductions of 212 bird species, of which a significant number were waterfowl, game birds, pigeons and parrots. In terms of the geographical distribution of introductions, about 60% were on oceanic islands, 20% on continents and 20% on continental shelf islands.

INTRODUCTION OF EXOTIC ANIMALS AND BIRDS AND THE EFFECTS ON THE INDIGENOUS ECOLOGY

3. The author identified 6 principal types of ecological effect:

- damage to plants or habitat;
- imbalances in prey caused by predation;
- introduced species using resources needed by indigenous species with or without competition effects;
- the spread of parasites or disease;
- breeding with indigenous species to produce hybrids;
- the introduced species becoming an additional source of prey to indigenous species.

He summarised the proportion of introductions, expressed as a percentage of the total number of introductions of mammals or birds respectively, which have caused an ecological effect, dividing them into three categories. His findings were as follows:

Kind of ecological effect	Mammals %	Birds %
Plant and habitat damage	20	0
A significant impact on native species by predation	17	1
A significant impact on native species by competition	3	3
Total proportion of introductions causing an ecological effect	40	5

DUTCH ELM DISEASE

1. The loss of elms from the latest outbreak of Dutch elm disease([5]) transformed the English landscape. Yet it has not been demonstrated that, as a consequence, any British species of animal or plant has been driven to extinction. Some insect species closely dependent on elms may, of course, have been lost without anyone noticing; and the position of others may have been made more precarious (for example the white letter hairstreak butterfly which has caterpillars that feed on elms). In many places elms were the predominant woody plants of hedgerow. Many hedges were lost through the death of elms from the disease. Larger changes in the populations of plants and animals, commensurate with the change in appearance of the landscape, might have been expected. That these have not been observed is no cause for complacency. It may simply reflect how little investigation has been carried out and how little is understood about indirect effects in ecological systems.

2. There have, of course, been some further effects. The best documented examples are for birds([45]). Several species of farmland birds that require high song-posts (for example the chaffinch) have decreased as elms have disappeared. In other cases loss of elms has directly removed feeding sites and may be linked to reductions in populations of such species as goldcrests, willow warblers and chiffchaffs. Yet the woodpigeon, which appeared to be heavily dependent on elm blossom buds as an early spring food, remains abundant. Some species have lost feeding sites indirectly; once elms go, more light penetrates to the bottoms of hedges, the vegetation there grows more thickly and species such as robins and dunnocks, which need bare ground to feed on, decline. Increasing light penetration also makes hedges less suitable as nesting sites for long-tailed tits, and this species may be lost completely as a breeding species from badly affected areas.

3. Temporarily, some bird species feeding on the insects frequenting dead and dying wood increased, for example nuthatches and woodpeckers. In the longer run, species requiring high, safe nesting sites in tree holes (for example the jackdaw, kestrel, tawny owl, barn owl and stock dove) have all declined where there are no alternative nesting sites. Barn owls have declined most seriously. The effect on the food web of the changes in populations of any of these species is unknown. Nothing drastic appears to have happened but, if voles increased because kestrels and owls declined, who would think to blame the pathogenic fungus carried by a beetle, several steps away in the web?

vegetation and scrub have taken over. The box opposite describes some of the wider consequences of myxomatosis in the UK.

4.22 The introduction of an exotic as part of a pest control programme in Hawaii illustrates other unpredicted consequences with wide environmental effects. Parasites were imported to control moths which damaged crops. The parasites also destroyed many of the caterpillars of Hawaii's butterflies and moths. This led to the rarity and perhaps extinction of natural enemies of the native caterpillars, especially the *Odynerus* wasps, and of Hawaii's native insectivorous birds([2]).

4.23 These cases also raise the issue of monitoring the effects of introductions. Birds and butterflies are of general interest and their loss is noticed but, if the affected species in Hawaii had been of little public interest, the effect of the introduction might have gone unobserved. Even when highly visible species are affected, it may not be easy to identify the cause of the decline. The longer it takes to detect the problem and trace the cause, the smaller the chances of remedy.

RABBITS AND MYXOMATOSIS

1. The introduction and spread of the Myxoma virus in the UK had many indirect environmental effects because rabbit populations interact strongly with their food plants. The removal of rabbits markedly changed the structure and composition of vegetation, with a wide variety of effects on other species. Some of the examples are anecdotal but serve to illustrate the kind of complex and unexpected things that can happen. As grassland sward became taller and thicker, ant populations declined. These ants are important prey for green woodpeckers, and a decline in green woodpecker numbers has been attributed, at least in part, to the effects of removing rabbits([46]). It is not known whether any prey of green woodpeckers such as woodboring beetles then increased but it is possible that some did. It would not have been easy, prior to the release of Myxoma virus in Britain, to predict the consequences for woodpeckers or indeed for the wood-boring beetles.

2. Better documented examples include the decline of open country or heathland species of high conservation importance, such as stone curlews and the large blue butterfly, in both cases attributable at least in part to changes in the vegetation. As rabbit populations collapsed predators, such as buzzards and foxes, turned to alternative prey, for example mice and voles. The indirect effects on other organisms of this increased predation on rodents is unknown. In woodlands, due to the lack of rabbits, sycamore seedlings survived in unprecedented numbers. The first few years after the introduction of the Myxoma virus saw a whole generation of this introduced tree dominating in woodland glades and shading out the existing plants.

Traditionally bred plants and animals

4.24 As noted in Chapter 2, cultivated plants and domesticated animals have been bred for centuries in order to improve their value to man and have been introduced widely into the environment. Some GEOs may be expected to have similar impacts on the environment to those produced by new varieties of traditionally bred crops and ornamental plants. In breeding programmes in agriculture and floriculture large numbers of progeny from sexual crosses are released in field trials for evaluation. The diversity of types in these progeny is often enormous, but most of the offspring are unsuitable for use in commercial agriculture and horticulture. When a successful plant has been selected its seed is multiplied and ultimately is made available for sale. If a new cultivar of a commercial crop is highly successful it will be grown on large acreages. This routine practice obviously has significant effects on the environment.

4.25 Many traditionally bred genetic variants released into agriculture are chosen because they have genes improving resistance to pests or pathogens by comparison with the cultivars they are intended to replace. Such effects will also be the desired aim with many genetically engineered crop plants. When resistant varieties are adopted by the industry they are expected to have significant impacts on local population dynamics among other organisms in the environment, namely, the pests and pathogens to which they are resistant. In general, however, the animals or plants produced by conventional breeding techniques are not perceived by the public as a threat to the environment.

Ferals and weeds

4.26 Many domesticated animals and crop plants cannot survive for long without man's intervention. Some domesticated animals have, however,

established self-sustaining populations in the wild, known as feral populations. Often ferals, like weeds, have become pests. The severity of the problems which they pose varies. Fish from fish farms frequently escape, sometimes causing damage to local aquatic life and raising fears that these strains will displace wild types to the ultimate detriment of fish stocks([102,161]). Potatoes and other crops are common weeds in following crops, although potatoes are unlikely to become major pests in the UK because they are susceptible to blight and late frost damage. In less than two decades since it became a widespread crop, oilseed rape has colonised non-agricultural land, particularly roadsides. In addition to landscape effects, these plants now represent a source of genetically mixed pollen which may impede efforts by the farming community to introduce improved strains of oilseed crop plants (Plate 7).

4.27 Oceanic island environments are particularly sensitive to invasion([44,36]). There are many examples of ferals and introduced domesticated animals that have caused extensive damage([100]). The effects of goats on the native flora and hence the fauna of Hawaii([101]), the Galapagos and sub-Antarctic Islands are well known examples of this.

The man-made environment

4.28 The examples given above have illustrated the impact of released organisms on the environment. Much of the earth's land surface, particularly in Britain and continental Europe, shows the effects of human activities. Not only are built-up areas artificial environments but the wider countryside itself is also a product of changes introduced, directly or indirectly, by agriculture, forestry, industry, leisure, transport and other activities. Indeed, changes are being introduced continually under varying degrees of control and with differing levels of controversy. Such changes raise issues of amenity and land use policy as well as of conservation. Many of the resultant man-made environments support a varied flora and fauna, are much cherished and require continued intervention or management to ensure their perpetuation. For example, nightingales nest chiefly in coppiced broad-leaf woodland, nightjars in clearings in conifer forests and golden orioles, in England, in hybrid poplar plantations. The local abundance of these birds in Britain is dependent on the continuation of the man-made habitats that support them.

4.29 Another consequence of man's activities is that large populations of the same species have been brought together in some of these environments — people in cities, plants and animals on farms, fish in fish farms, trees in forests. Such groupings are more susceptible to epidemics of diseases, pests and parasites than natural mixed populations([23]). They therefore require continued protection in order to survive.

CHAPTER 5

ASSESSING THE RISKS

Introduction

5.1 Chapter 4 illustrated some of the environmental impacts that might arise from the release of genetically engineered organisms. As is pointed out in that chapter, many of these are hypothetical or based on analogies whose applicability to genetic engineering is a matter of debate. In other fields, the most reliable information about risks usually comes from practical experience supplemented by controlled experiment. With genetic engineering, however, no practical experience of large scale releases to the environment exists as yet and only a small number of restricted field trials have taken place. While these are of use in assessing risks presented by the release of GEOs, analysis of such risks must rest primarily on information from contained experiments, knowledge of the parent and related organisms, and understanding of ecological and other biological principles.

5.2 During the course of our study a number of authoritative reviews have been published of the risks associated with the release of GEOs. These include a statement by committees of the International Council of Scientific Unions([47]) and reports by the United States National Academy of Sciences([48]), the US Congress Office of Technology Assessment (OTA)([8]), the Ecological Society of America([49]) and a number of others([70]). In this chapter we discuss the main issues that have emerged from these reviews, from other literature and from the evidence that we have received which has been influential when formulating our recommendations.

The resilience of the environment

5.3 Changes to the environment caused by some alien (or exotic) animals, plants or micro-organisms have been described (paragraphs 4.14–4.23). Natural communities are in general resistant to invasion by alien species. For example, gardens in Britain contain many thousands of species and varieties of non-native plants, but few of them escape and establish themselves in the wider countryside. Likewise, existing natural communities are resistant to invasion by most crops and domestic animals. Since the 19th century, thousands of tons of the bacterium *Rhizobium* (paragraph 2.20) have been added to soils worldwide with no observed adverse effects([92]).

5.4 The environment has the capacity to recover from many disturbances. For example, it is common practice in horticulture to sterilise soil before planting in order to reduce pathogens. The grower may subsequently add some beneficial fungi to help his crops but, even without this, the appropriate bacteria and fungi gradually reappear and nutrient cycling and other essential functions are restored([50]). There were serious environmental consequences from the gales in South East England in October 1987. Along the south-facing ridge of the North Downs, for example, thousands of trees were blown over with conspicuous damage to the flora of the woods which cloak the ridge. Already, however, wild flowers, particularly foxgloves, are invading the clearings created by the wind-thrown trees and tree seedlings have regenerated. It may be many years before the damaged environment recovers to its former state but the woodland plant community has displayed a natural resilience.

5.5 The two main reasons for alien or domestic organisms failing to become established in natural communities are, first, that they are ill-matched to the

climate and other physical conditions and, secondly, that the prevailing biological conditions exclude them. For example, there may not be enough nutrient of the right kind; established native species may be more effective competitors; resident enemies and diseases may preclude invasion; or there may be insufficient space available to newcomers.

5.6 One measure of the degree to which natural communities are susceptible to invasion was provided by Williamson and Brown whose paper([51]) reported that, of 1058 documented invasions or introductions of alien species of plants (including crop and garden plants), animals or micro-organisms into the British Isles, about 1 in 10 became established. Of these approximately 1 in 10 have become pests, varying in severity from relatively minor to highly damaging. Comparable data exist for the United States([8]). However, most failed invasions, particularly of smaller organisms, are likely to go unrecorded so that the probability of an invader becoming established is much less than these figures suggest. Moreover, none of the heterogeneous collection of invading organisms identified in the study by Williamson and Brown had been screened for safety prior to arrival and yet 90% of those species that became established have not become pests.

5.7 An important factor contributing to the resilience of the environment in relation to micro-organisms is the diversity of habitats that exist in nature. For micro-organisms, soil provides an enormous variety of habitats and any one species can colonise but a few. A typical handful of soil will contain a large number of micro-organisms (as many as 10^{10} bacteria in each gram of soil) comprising many types with a wide range of differing nutritional requirements, preferred temperatures for growth, abilities to tolerate acidity, needs for oxygen and other characteristics([96,97]). It is inherently unlikely that a micro-organism could be engineered so that it would dominate more than a small proportion of the wide range of habitats to which it would have access. However, it would be wrong to assume that a high diversity of species necessarily protects communities from invasion. The Cape Floral Region of South Africa is one of the richest in the world; yet it has proved to be extremely vulnerable to invasion by exotic plants, for example Australian woody bushes of the genus *Hakea*, pine trees and acacias. By aggressive invasion these exotics threaten large numbers of native species of plants with local, or in some cases total, extinction([52,53]).

5.8 We conclude that, although the environment is generally resilient, resistant to invasion by alien organisms and robust to biological perturbations, it is probable that some organisms, once released to the environment, will become established. Most are likely to pose no hazard but others may cause varying degrees of disturbance which, in the extreme, could have serious environmental consequences.

5.9 Another important aspect of the environment that needs to be considered is the resilience of the major biological and geochemical processes. Processes such as climate patterns and the cycling of carbon, nitrogen or other nutrients through the environment are essential to the living environment as we know it but they are only imperfectly understood. Paragraphs 4.8 and 4.9 discussed the possibility that releases of GEOs might interfere with these processes. A significant disruption of them, even locally, might produce a major environmental impact. A recent survey([8]) has concluded, however, that they are unlikely to be at risk from any releases of GEOs expected to take place in the near future.

Uncertainty in predicting environmental impacts

5.10 The prediction of environmental impacts is difficult. The science underpinning predictions about invasions is not well developed([54,55]). There

are many examples of small groups of closely related species in which one of the group has become established in a new environment while the others, despite apparently equal opportunities, have not. In Britain, for example, introduced Mandarin ducks (*Aix galericulata*) have done well and are spreading whilst introduced Carolina ducks (*Aix sponsa*) are not[46]. Paragraph 5.7 refers to a species of *Hakea* which has become a major weed in South Africa; three other species of this bush are established there but have not become pests. Similarly, *Avena sativa* is an important crop (oats) that has not spread outside the fields where it is grown and the closely related *A. strigosa* is a fodder crop on poor soils and a minor weed; another close relative *A. fatua*, on the other hand, is a troublesome weed of arable land[2]. It is extremely difficult to determine why one species becomes a pest while one or more of its close relatives fails to do so. Another example of the difficulty of prediction is afforded by *Vulpia*, a rare British native grass which has become a major introduced weed in Australia. A detailed study[56] on the ecology of the plant in Britain offers little predictive insight into its dramatic change in status in Australia[54].

5.11 In some circumstances, particularly with micro-organisms, behaviour can be examined in the laboratory. Indeed, what is known of the biological properties of bacteria has normally been determined from laboratory work with single-species cultures. The knowledge of the interactions of most species of bacteria in mixed populations in natural ecological systems is, however, extremely limited[57].

5.12 There is growing evidence to support the hypothesis that many populations exhibit threshold behaviour, with one outcome if numbers are below a critical value but another if they are above it[49,57,58]. For example, below some critical threshold density, populations may die out whatever is done to try to save them[59]. The probability of establishing a new population of insects for the biological control of pests is higher the greater the number of insects that are released[60]. The difficulty of predicting how GEOs will behave in the environment is increased by the existence of these threshold levels in natural populations.

5.13 Many release proposals will be concerned with domesticated animals and crops whose behaviour is much better understood than any of the wild species mentioned above. In such cases it should be possible, by thorough evaluation, to make a reasonable prediction of the likely environmental behaviour of the organism. A genetically engineered wheat, for example, planted in similar conditions to normal wheat, is likely to behave in a similar manner to its non-engineered relative. The same will be true of well known micro-organisms such as *Rhizobium*. Also, the knowledge that certain plants often become weeds, that certain animals can be major pests and that certain micro-organisms can be harmful, together with experience from the release of exotic species (paragraphs 4.14–4.23), will help to narrow the areas of uncertainty. We discuss in paragraphs 10.29–10.32 research which would help to improve further the ability to predict the behaviour of organisms in the environment.

5.14 In general, the ability to predict the outcome of a release is likely to be greater if the GEO to be released is a modified version of an organism common in the locality of the release; the behaviour of that organism in the environment is well-known; the genetic modification is limited in scope; the properties of the new genetic material and its interaction with the original organism are well understood; and the quantities to be released are not excessive.

The analogy with traditional breeding methods and natural processes

5.15 It has been argued that genetic engineering is simply a more controlled and advanced means of producing new constructs than the traditional breeding techniques used by man for centuries([149]). Traditional breeding techniques enable some strains, which have not occurred naturally and become established, to be developed and marketed. In general, however, traditional techniques are limited to organisms that can cross-breed and that are thus related to each other. Genetic engineering, by contrast, allows genes from almost any organism to be introduced into almost any other organism, regardless of sexual compatibility or evolutionary relationship([48]). In this respect genetic engineering is qualitatively different from traditional techniques.

5.16 It is sometimes argued that all possible genetic combinations have occurred during evolutionary history and that organisms with novel traits cannot therefore be produced by manipulation of genetic material. This has been refuted([57]). In any case, many of the combinations that have arisen naturally will have done so as isolated events in environments which did not favour their survival([48]). Genetic engineering, by contrast, enables specific, planned changes to be made in the laboratory. Multiple modifications which are unlikely to happen together in nature can be made. As in conventional breeding, modified organisms, that might not survive if they resulted from mutation in the wild, can be reproduced in the laboratory under favourable conditions until they are sufficiently numerous to increase their probability of survival on release([152]). The organisms may then be released into an environment deliberately chosen to improve their chances of survival. In this way GEOs may have a potential to establish not found in organisms that have arisen naturally.

5.17 It is sometimes argued that organisms that have had a gene deleted by genetic engineering should be considered as safe because gene deletions occur commonly in nature([95]). We do not share this view. A deletion could profoundly alter the behaviour of an organism. For example, deletion of a promoter, enhancer or suppressor could alter the extent, timing and location of the expression of a gene. Techniques such as those described in the preceding paragraph could then ensure survival and reproduction of the organism in very large numbers resulting in an environmental impact that would be most unlikely to happen naturally.

5.18 The full consequences of genetic engineering cannot be foreseen. It is possible now to do things which were inconceivable 20 years ago. Ingenious people in the future may be able to use the tools at their disposal, for example, the ability to construct novel genes by chemical synthesis, to develop organisms whose impact may be quite unlike anything previously known.

The 'fitness' of genetically engineered organisms

5.19 A frequently expressed view is that GEOs will almost invariably be 'weaker' and less fitted for survival than naturally occurring organisms([57,87]). This argument is sometimes supported by reference to the so-called 'excess baggage hypothesis', which argues that the addition of genetic material imposes a burden on an organism by requiring more energy to carry and express the additional genes([90]). As a result, the organism would be at a disadvantage compared to its natural relatives and would, therefore, either fail to compete successfully or be under pressure to shed the extra genetic material. There is, however, no general support for the excess baggage hypothesis; indeed, some soil bacteria, such as *Rhizobium*, contain

about a quarter of their DNA in plasmid form([98]), much of which appears to be redundant([50]). In general, any burden that additional DNA might impose would have to be set against any compensating advantage.

5.20 Stronger arguments in favour of the intrinsic weakness of GEOs stem from observation of the viability of organisms in the wild. Modern artificially bred plant varieties are often incapable of extended survival in the environment without human intervention to protect them. It has been put to us that genetic engineering for agricultural purposes is unlikely to change this characteristic because to do so would offer no commercial advantage. Industry is unlikely to be interested in deliberately introducing organisms which might spread uncontrollably or find a permanent niche in the environment([81,83]).

5.21 Many crops, however, such as the potato, can be a weed in following crops. The potential of the potato to become a serious, persistent weed is limited by its susceptibility to blight and to late frost. Were such limitations to be removed by genetic manipulation and coupled, for example, with the introduction of herbicide resistance, the plant that resulted could be a major nuisance([54]). It might be argued that no reasonable person would release such a plant. It cannot prudently be taken for granted, however, that industry or other researchers, left entirely to their own devices, would necessarily eschew introductions that presented an unacceptable degree of risk or would avoid blundering into them.

5.22 Evaluation of the 'fitness' of organisms also has to take into account evolutionary processes. All interventions in the natural world are undertaken against a background of continuing change. The efficacy of particular pesticides and antibiotics, for example, declines as the target organisms evolve and develop resistance. Similar processes may limit the benefits accruing from releases of GEOs. Equally, after release GEOs may themselves adapt in response to natural selection pressures just as the Myxoma virus, released in Britain and Australia in the 1950s to control rabbit populations, evolved to become less virulent([61]). The course of evolutionary adaptations may not be easy to predict. There is increasing evidence that selection can act, in complicated ways, on related sections of the genome. In a recent laboratory experiment a bacterial population evolved from an initial state where extra genetic material reduced its competitive fitness to one where the same genetic material conferred a competitive advantage([58,90,93]).

Gene transfer

5.23 A much discussed anxiety is that genes inserted into new host organisms may transfer after release to other organisms with undesirable consequences([8,48,94]). The extent to which genes, especially novel genes, may spread is an important uncertainty in assessing the risks in the release of GEOs. In some circumstances genes may move from one organism to another as, for example, plasmids (paragraph 3.5) move between bacteria([92]). Genes may also move through a population by processes of natural reproduction. For example, a genetically engineered animal may breed with a non-engineered animal and the offspring may inherit an introduced gene. Genetically engineered plants may disperse introduced genes through pollen transfer([89]).

5.24 The development of herbicide resistant plants has raised concerns about the possibility of gene transfer. Evidence we have received([81]) has pointed out, however, that most inserted genes are likely to be ones that already exist in nature, albeit in other organisms. When this is the case,

release of the GEO may produce only a slight increase in the number of such genes which are in the environment and potentially available for transfer. Nevertheless, concerns may still arise. One hypothetical example put to us in evidence would be the introduction into maize of the gene for the highly toxic protein, ricin, from the castor oil plant([81]). This would pose a major risk to the lives of people and animals if the protein were produced in parts of the maize plant eaten by them. Even in locations in which the gene was naturally abundant, for example where castor oil plants are common, this would still be the case.

5.25 In other cases, however, the potential hazards may be less than might appear. For example, organisms containing cellulase genes will break down cellulose, a major component of wood. It might therefore seem undesirable to release novel micro-organisms containing cellulase genes. In fact these genes are already widespread in the environment([81]), in organisms responsible for one part of the carbon cycle, but living trees are not decomposed. Such a proposed release would have to be carefully assessed to ensure that there was no significant risk but there need be no *a priori* presumption against it.

5.26 A high concentration of genes does not, of course, imply that gene transfer will occur on a substantial scale. The bacterium *Bacillus thuringiensis* (Bt) contains a gene, which can be on a highly mobile plasmid, producing a substance toxic to many insects. This, combined with the fact that populations of *B. thuringiensis* become very large in insects that they kill, might be expected to create an opportunity for the gene to transfer to other bacteria. So far as is known, the toxin gene is not widespread in other bacterial species. This suggests that movement is rare despite the theoretical ease of transfer or that the gene is not advantageous to recipient bacteria([107]). If the Bt toxin gene were inserted into plants, it might, however, spread to other plants through pollen transfer. Two consequences could follow: insects other than the original targets might become affected and selection pressures for resistance to the toxin would increase.

5.27 Traditionally bred crops frequently have traits such as disease resistance and insect resistance bred into them. Despite the ability of pollen to transfer the relevant genes to other plants (which would then have a selective advantage) problems such as insect resistance are not known to have emerged. Nevertheless, with any newly engineered organism it will be prudent to begin with the assumption that an introduced gene is capable of spreading widely and then to challenge that assumption.

The risk of creating dangerous organisms

5.28 A particular concern is that genetic engineering could convert non-pathogens into pathogens. Pathogenicity involves the combined effects of many genes. A pathogenic micro-organism needs to be able to attach itself to cells of a host organism, to resist the defence mechanisms of its target, to create toxic products or other attacking mechanisms, to spread from one host to another and to survive between hosts([35,48,81,88,92]). There are, however, non-pathogenic micro-organisms which already possess most of these characteristics and care will then be needed to ensure that small changes to their genes have not inadvertently taken the last step to turn them into pathogens. Another possibility is that an avirulent form of a pathogen might be made virulent by a simple genetic manipulation([8]), or an existing pathogen might have its host range broadened([88]). Likewise a strain of, for example, *Escherichia coli* that had been made non-pathogenic by removal of a gene could have its pathogenicity restored by reinstatement of the gene. In some plant viruses the presence of a single gene diferentiates the avirulent form

from the virulent[62]. Deletion of that gene would make the virus more virulent in its effect on certain plants. A change in a single gene could also alter the range of plants attacked by particular viruses[48].

5.29 As with pathogenicity in micro-organisms, 'weediness' in plants normally depends on a large number of genes. Some crop plants, however, already contain many of the appropriate genes and may, indeed, be related to known weeds. Oilseed rape and oats have already been referred to in this context (paragraphs 4.26 and 5.10). Small genetic changes could significantly enhance the potential for such plants to become weeds[48].

5.30 We conclude that the risk of inadvertently converting harmless organisms into environmentally deleterious ones appears to be low. However, when organisms which already possess some of the necessary genes are being manipulated, they need to be scrutinised to ensure that they have not been converted into a threat to man or the environment.

Viruses

5.31 Mention has been made in earlier chapters (paragraphs 2.24, 3.12 and 3.15) of genetic engineering involving viruses, either as vectors to insert genes into other organisms or as objects of manipulation in their own right. Viruses arouse special concern because some are associated with serious diseases in man, in other animals or in plants and because there are few drugs for the treatment of viral diseases.

5.32 The genome of a virus can be so small that one gene can represent as much as 25% of the total. In contrast, in animals, plants or even bacteria, one gene may represent no more than 0.001% to 0.1% of the genome. A change in one gene of a virus may therefore have a more significant and perhaps unexpected effect on a virus's characteristics, for example, on host range, virulence or persistence, than would a change in one gene of a plant or animal.

5.33 Some viruses, particularly retroviruses (Appendix 4), are able to transfer genes into a host's genome, including germ-line cells, in which expression may be detected in subsequent generations. This makes them useful as vectors in genetic engineering, particularly of animals. Risks arise, however, from the possibility that this process may also activate adjacent sequences in the host's genome (Appendix 4 paragraph 15). In addition, retroviruses can copy host genetic material and incorporate it into their own genomes. This could alter the characteristics of the retrovirus, for example by extending its host range or enabling it to gain some other unexpected trait. The guidance on work involving retroviruses published by the Advisory Committee on Genetic Manipulation[63,68] is designed, amongst other things, to prevent such problems arising.

5.34 Concerns about viruses have led some, including a Commission of Enquiry in West Germany[75], to recommend that genetically engineered viruses, other than vaccines, should not be released at all at present (paragraph 9.6). Not all viruses cause disease, however. Work with those that do is subject to the legislation controlling the handling and release of pathogens, whether they affect humans, animals or plants (paragraphs 7.14–7.16). In many circumstances, as illustrated in the example in paragraph 2.24, viruses offer the potential for safe, useful products. Provided that the release of retroviruses, or of organisms manipulated using retroviruses, is approached with the utmost caution, we see no reason for imposing new restrictions relating specifically to genetically engineered viruses.

Experience of GEOs in the laboratory

5.35 Early in the development of the science of genetic engineering, researchers called for a moratorium on certain types of laboratory experiment

which might create unknown or unexpected hazards([64]). Discussion of the risks led to arrangements for containment of experiments according to the degree of perceived risk([65,66,67]). Despite widespread laboratory activity on GEOs and the acknowledged risk of accidental release, no case has come to our attention in which harm has been shown to have resulted from the use of GEOs. The absence of problems has led to a greater confidence amongst practitioners and regulators and a gradual relaxation in the stringency of containment requirements([35]).

5.36 Although the initial anxieties have not proved founded, experience has demonstrated that a timely, careful, considered response to potential risks is an effective basis for safe operation. Research is now moving out into the wider environment and, although knowledge about the behaviour of GEOs in the laboratory is much greater than it was, there are still large gaps in knowledge of behaviour in the field.

5.37 The responsible manner in which scientists worldwide addressed the early concerns did much to create confidence for further development of the science. An initially cautious approach, which could then be relaxed in the light of experience, was the path adopted then. It is the responsible way forward now as scientists move into a new phase of the technology with a different set of targets and hazards. Scarcely a month passes without the discovery of some unexpected aspect of the genetic process. This has the positive consequence that the more that is known about what happens in nature, the better placed society is to avoid harmful releases, provided that the new knowledge is taken into account when releases are planned. New discoveries also, however, open the door to more ambitious and more fundamental interventions in natural processes with the possible emergence of new risks to the environment. It is not sufficient to develop a system of controls for the release of genetically engineered organisms on the basis solely of what is currently possible. It is necessary also to take into account, as do our proposals in subsequent chapters, the ingenuity that scientists will apply in the development of new organisms.

The recovery or eradication of GEOs after release

5.38 A major concern is the difficulty, should it prove necessary, of eradicating after release a genetically engineered organism or genes that may have spread from a GEO to other organisms. Animals, plants and micro-organisms will pose different problems. Large animals such as sheep or pigs are generally readily recoverable. Recent experience with coypu in East Anglia, following escapes, demonstrates that eradication of a smaller mammal is sometimes possible, but the effort may be prolonged and the cost high([2]). Animals such as birds, fish, small mammals and insects are more likely to be irretrievable once released.

5.39 Eradication of whole plants, genetically engineered or otherwise, should normally be possible using mechanical methods or herbicides. It will be important when introducing resistance to particular herbicides into plants to ensure that other herbicides which kill the plants remain available([54,81]).

5.40 Once a genetically engineered crop plant variety has been released commercially it may be used in traditional breeding. An inserted gene could then be spread into different, albeit related, plants with consequences that might not have been anticipated when the original plant was released. By traditional crossing of engineered plants, progeny with multiple introduced genes may result. Common selectable marker genes (paragraph 3.13) associated with introduced traits will proliferate too, resulting in different combinations of introduced genes with little knowledge of their sources or of

their effects. For example, one company might insert a gene conferring resistance to the antibiotic kanamycin as a selectable marker alongside a useful gene on, say, chromosome 1 of a plant. Another company might insert the kanamycin resistance gene alongside a different useful gene on chromosome 2. Breeders might then cross the two plants. From several rounds of crosses, as is usual in breeding programmes, plants might emerge containing many kanamycin resistance genes as well as other, useful genes. Eradication of an introduced gene under such circumstances could be extremely difficult. We received evidence of a case of traditional breeding technology which resulted in the inadvertent introduction into wheat of a gene detrimental to the wheat's bread-making qualities in association with a gene introduced to confer disease resistance. The unwanted gene proved difficult to eradicate([62]).

5.41 Because of the way in which the international plant breeding industry operates it would be prudent to assume, when considering a commercial release, that a gene in a crop plant may be transferred by breeders into any other related plant. This has implications for which international measures are required. Viable samples of current commercially-used plant varieties should be conserved so that it will be possible to return to these in order to eliminate an undesirable trait if necessary. There should be lineage registers which record the history of plant varieties, including information on any introduced genes. In addition, before organisms with introduced genes are released, the introduced DNA sequence of the new genes should be characterised for future reference.

5.42 The recovery or eradication of released micro-organisms raises different issues. The smallpox virus has been eradicated worldwide, but was a special case in that it had no host other than man, the disease spread slowly, clinical diagnosis was highly efficient and there was an effective and practicable vaccine available([32,69,91]). Vaccination is, however, a proven preventive measure for many cases. It is being attempted in continental Europe to try to limit the spread of rabies([71]). Outbreaks of foot-and-mouth and some other animal diseases in this country have been dealt with by containment and extermination([20,32]). In general, however, eradication is difficult, costly and not always successful. Particular problems arise where the micro-organisms have dormant stages such as spores, as with anthrax. In such cases only sterilisation of an infected area is likely to offer confidence that the micro-organisms have been eradicated([54]). Formaldehyde was used by the Ministry of Defence recently to decontaminate Gruinard Island where experiments with anthrax had been carried out([72]).

5.43 The extent to which a GEO, or genes that might spread from a GEO to other organisms, can be recovered or eradicated from the environment will be an important factor to consider before a release takes place. Genetic engineering offers the opportunity to debilitate organisms so that they are unable or less likely to survive in the environment. This should be done where practicable, as discussed in paragraphs 6.26 and 6.27.

Free DNA in the environment

5.44 Like all the components of living systems DNA is a chemical. The molecules are chains built out of four different simple building blocks. The prime biological function of DNA is to carry information (paragraphs 3.3–3.8). To become biologically active DNA must be taken up by cells in a special way and become integrated into the genetic apparatus where, if it carries all the correct signals, its genetic information can be expressed([73]).

5.45 Large amounts of DNA are added to the environment as a result of the natural processes of excretion, death and decay of animals, plants and micro-organisms. This is referred to as free DNA. For example, the human population alone of Great Britain deposits every year about 100 kilograms of DNA of the common intestinal bacterium *Escherichia coli*. This DNA, like most other common biological material, is generally rapidly degraded[73]. In some parts of the environment, however, for example in clay soils[148] and in estuaries[105], this DNA can be absorbed on particulates and becomes more resistant to natural degradation[103,148]. Experiments, largely performed in the laboratory with special bacteria which have natural mechanisms for DNA absorption, have shown that DNA can be taken up and integrated into the genetic material[104,106]. Very little is known about the frequency of this in the environment or its consequences, but it could be important in the persistence and spread of DNA in the environment.

5.46 It is possible that, as genetic technologies develop, exceptionally large amounts of specially constructed DNA molecules associated with known toxic effects may be produced. Care must then be taken in their disposal especially if they have the capacity to become converted into novel pathogenic agents. In addition, chemically modified nucleic acid molecules may be synthesized which have all the essential properties of DNA but resist biodegradation[73]. Similar considerations as are discussed in this section apply to RNA.

Way forward

5.47 This chapter has discussed several issues relevant to the safety of releasing GEOs to the environment. In subsequent chapters we set out our views on the procedures and legislation necessary to ensure that the environment is adequately protected against risks. We propose a precautionary but realistic system of regulation. This should allow safety issues to become part of the development of the technology rather than having to be introduced following problems. Some may consider our proposals onerous but we believe them to be necessary for the protection of the environment. Moreover, the biggest brake on the environmental application of genetic engineering could result from an inadequately scrutinised release which caused serious damage to human health or to the environment and destroyed public confidence in both the science and the scientists. Those involved in genetic engineering generally recognise that their interests would be best served by a sensible and objective system of control. We consider that our recommendations in the following chapters meet this need and will be capable of adaptation as knowledge increases so that they will not unreasonably impede the application of new technology.

5.48 It seems likely that, in many situations, biological products could be safer and less polluting than non-biological alternatives, for example offering more selective control than chemical pesticides with less harmful residues[35]. We have received evidence, however, suggesting that broad range biological control might be favoured on economic grounds over selective products since the commercial market for the latter will be smaller than for broad range products[74]. A selective, readily degradable chemical pesticide leaving no objectionable residue and which is non-toxic to humans, could it be designed, might have an advantage over biological products. Research in this direction should not be abandoned in the enthusiasm for biological control. The development of agricultural practices such as integrated pest management, which may help to reduce the scale of the problem with which pesticides are trying to deal, should also continue to receive attention.

5.49 We are conscious that the imposition of strict controls on the release of genetically engineered organisms may increase incentives to select and

develop non-engineered organisms, particularly perhaps micro-organisms. The impact of naturally occurring organisms in new environments can be major, as described in Chapter 4. This potential may become all the greater as technologies for the selection, development, production and use of non-engineered organisms become more refined. The result could be a threat to the environment as great as that posed by some GEOs and we recommend in paragraph 8.30 that this should be considered further.

CHAPTER 6

PROCEDURES TO MINIMISE RISK

Introduction

6.1 The procedures we recommend in this chapter to reduce the risk of harm to the environment reflect the discussion in the preceding chapter of issues raised by the release of genetically engineered organisms. The recommendations are generally in line with existing UK procedures adopted by the Health and Safety Executive (HSE) and its advisory committee, the ACGM, described in Chapter 7. Where the recommendations go further than current practice, for example in relation to risk identification and to monitoring, we consider them to be necessary because of the size of the potential problem. We believe that it is possible to have effective procedures which are not unduly onerous and we have framed our recommendations accordingly.

A moratorium

6.2 A report to the West German Parliament([75]) has recommended an initial five-year ban on the release of genetically engineered micro-organisms containing foreign genes. It argues that the behaviour of such organisms in the environment is not yet sufficiently well understood for there to be confidence about the safety of their release. It also recommends a programme of research to increase knowledge about their behaviour. The European Parliament has recently adopted a report which amongst other things calls for a moratorium, and consideration of a total ban, on the release of genetically altered organisms([146]).

6.3 We have considered whether to make a similar recommendation. Organisms which are pathogenic are already the subject of legislative controls in this country, as described in the next chapter. Genetically engineered organisms will come within these systems of control where appropriate. Many other organisms, including micro-organisms, are harmless or even beneficial and there is no reason why the insertion of foreign genes should necessarily turn these into harmful organisms. Many of the issues relating to the behaviour of organisms in the environment are not readily susceptible to research in laboratories or in contained artificial environments but require localised and carefully controlled experiments in the field. Arrangements which allowed such experiments to be carried out, incorporating careful monitoring and using GEOs which offered negligible risk, would make a greater contribution to safety than a moratorium. Accordingly, we do not consider that there should be a ban or moratorium on releases either in general or for specific categories. If our recommendations for controlling the release of GEOs are implemented, we consider that it should be possible to identify cases that raise concerns and deal with them appropriately on an individual basis, if necessary preventing them from taking place. We see no justification on environmental grounds for preventing releases which are considered safe from proceeding and our proposals would allow these to go ahead with any necessary safeguards.

Product controls

6.4 The case is sometimes made that, far from having a moratorium, there should be no new restrictions and protection against hazards should be achieved by reliance on existing product control mechanisms where these exist. It is argued that, if separate controls were set up for genetically engineered versions of such products, these would be subject to an unnecessary double scrutiny. It is further argued that, where there are no existing

product control mechanisms, as for example for crop plants, bacteria for leaching metal from ores or bacteria for cleaning contaminated land, it would be anomalous for products which were or which contained GEOs to be subject to control when others were not.

6.5 We agree that, where product controls exist, these should be the primary channel for assessing relevant genetically engineered organisms. For reasons discussed in the preceding chapter, however, we consider that GEOs raise issues which do not arise in other circumstances. Understanding of the behaviour of an engineered organism and how it might differ from that of a product prepared by more conventional processes is still at an early stage. GEOs therefore need an extra degree of scrutiny by people with particular knowledge of their behaviour and the ability to judge their environmental impact and who may not normally be involved in the product assessment process. The need for such a scrutiny arises, for the same reasons, where no product controls exist. In due course, accumulating experience may lead to a reconsideration of controls directed specifically at GEOs in favour of reliance on wider product controls. It would not be prudent to take this approach in the current state of knowledge. Any anomalies to which this may give rise should be accepted as part of the price to be paid for working at the frontiers of a new technology.

Scrutiny

6.6 The first consideration in the proper control of releases of GEOs is a thorough, expert scrutiny of every proposed release. This will reduce the likelihood of any untoward consequence of the release being overlooked and ensure that risks are recognised and responsibly handled. At this stage of the development of the technology, with limited experience worldwide of releasing GEOs, we consider that each case needs to be scrutinised by a national committee of experts subsequently referred to as the Release Committee. Prior to such scrutiny a local committee based within the organisation developing the GEO, which we refer to as a local safety assessment committee, should screen the proposal to ensure that only well thought out proposals come forward for national scrutiny. In due course it may be possible to identify types of release for which scrutiny could satisfactorily be delegated to these local level committees only. This has been proposed in the USA([76]). We do not consider that the UK should adopt such a procedure until considerably more experience of releases has been obtained.

6.7 It has been widely suggested that categories of organism should be drawn up and that proposals for release should be treated differently according to the category in which they fell. For example, the United States Environmental Protection Agency has proposed([76]) that, in micro-organisms, gene deletions and intra-organism gene additions represent a relatively low risk and could be subject to an abbreviated review procedure. Categorisation is a desirable and achievable objective. Given the lack of experience of releases of GEOs, however, and the certainty that the scope and power of genetic engineering will increase, it would be imprudent at present to define categories which may be exempted from scrutiny. We consider that case by case assessment of every proposal to release a GEO to the environment is essential. Categories are defined by points of similarity but, while these are informative, it is points of difference that are most important in considering the possibility of hazard.

6.8 The rejection of categorisation and insistence on a thorough case by case review need not result in undue burdens being placed on those conducting a release. Many release proposals will raise similar issues. Scrutiny can

concentrate on novel aspects of the environment or the organism. The extent and detail of information to be provided, beyond that required with the initial submission, will be less in cases which are well understood and will depend on the uncertainties inherent in the proposal, modified as necessary in the light of information acquired as the release progresses.

Assessment committees

6.9 Current proposals for release are likely to raise novel and varied issues. The effectiveness of any scrutiny process will thus depend heavily on the range and quality of experience and expertise that can be brought to bear upon the problem. As described in Chapter 7, the HSE and ACGM have set up a sub-committee of ACGM charged with the assessment of each proposed release. It is composed of experts from various disciplines and different public bodies such as the DOE, MAFF, NCC, Department of Health, Forestry Commission and NERC. We propose that this sub-committee should be reconstituted as an advisory committee in its own right to form the Release Committee and we elaborate in Chapter 8 on its responsibilities and membership.

6.10 Local safety assessment committees may not need the same range of expertise as the national committee but should contain ecologists as well as experts in genetic engineering. Other members with relevant local knowledge and expertise should be appointed where possible. Local authority environmental health officers could play an important role in representing local communities. We therefore recommend that local EHOs should be invited to serve on such committees. In order to make an informed contribution on a subject which is somewhat outside the range of current EHO responsibilities, training and advice will be needed and we are pleased to note that the HSE and the Institution of Environmental Health Officers have already made a start in this direction.

Information and assessment

6.11 The effectiveness of the scrutiny will depend not only on the expertise of those serving on the assessment committees but also on the quality of the information provided to them by those proposing to make the releases. Proposers will need to know precisely what will be required of them. The OECD published in 1986 a highly regarded and influential study of 'Recombinant DNA Safety Considerations'([78]). This identified, amongst other matters, the issues to be addressed in environmental and agricultural proposals for the release of GEOs. The OECD is currently developing its advice on assessing release proposals. The ACGM has published guidelines for proposers of releases in this country (paragraph 7.7) and the European Commission has put proposals to the member states of the European Community([6]). Other countries have also published information on their requirements.

6.12 The various proposals have much in common. It is clearly desirable that there should be international agreement on the information to be required of releasers and the procedures for assessment. At the time of writing, the ACGM is revising its guidelines for information and risk assessment to take into account experience with the releases which have occurred to date. We have seen a draft of the revised guidelines and endorse the approach that is being taken. We hope that the Government will use the final version as a model in international discussions on this subject. The key elements that need to be covered are:

(a) identity of personnel involved including qualifications and training;

(b) objectives of the release;

(c) location of the proposed release including relevant geographic and environmental information;

(d) description of the parent organism, any vector and the resultant GEO, including relevant biological and ecological information;

(e) description of the manipulation to produce the GEO, including its possible unwanted effects;

(f) arrangements for the release including preparation of the site, timing of the release, method of the release and any subsequent dismantling or decontamination of the site;

(g) potential environmental effects including information on any previous related releases;

(h) monitoring arrangements;

(i) contingency plans in case of unexpected events;

(j) results of prior local assessment and consultation.

6.13 The information submitted should provide convincing evidence that the proposer has carried out a thorough risk assessment of the proposed release and should also be sufficiently detailed for the Release Committee to make an informed judgment of the risks associated with the proposed release. Among the important issues covered should be: the extent to which the unmodified organism is native to the locality of the release; the pathogenicity or toxicity of the unmodified organism; changes in behaviour as a result of the genetic engineering, including changes in host range or virulence of organisms; the relationship between the GEO and likely predators, pests and prey; the stability of the GEO and the likelihood of gene transfer; the effects of dispersal of the GEO by wind or other means; the survival characteristics of the GEO including the ability to adopt dormant states; and the extent to which the GEO has been debilitated.

6.14 Some aspects of these issues may require experiments in laboratory or contained facilities but, even with these, it will not always be possible with current knowledge to provide firm answers about safety([99]). Research programmes in progress or planned should help to fill gaps in knowledge. We discuss this subject further in Chapter 10.

Risk identification techniques

6.15 Valuable as these approaches are, they need to be supplemented by a procedure that will encourage people to think of possibilities that might not otherwise have been considered, to test to the limit all possible outcomes and to minimise chances of overlooking significant hazards. In taking evidence for this Report we were impressed by the care and thoroughness with which those who were contemplating or advising on releases were tackling the problem of identifying the possible hazards. From previous studies, however, the Commission was aware of techniques, in particular the HAZOP (Hazard and Operability) study which has proved highly successful in exposing hazards in operating chemical plant. HAZOP has not, to the best of our knowledge, been considered in identifying the hazards of releasing genetically engineered organisms, though it has been successfully applied to the design and operation of a laboratory for contained experimental work([81]) and to the manufacture of a product using GEOs([82]). HAZOP provides a structured and systematic approach to the identification of hazards by enabling a team of experts concerned with the design and operation of plant to think imaginatively and

carefully about unplanned events that might arise. Further information is available from a number of sources including books by Kletz[79] and the Chemical Industries Association[80].

6.16 A HAZOP study proceeds by concentrating in turn on each element of the design (of the industrial plant) and using 'guidewords', such as NONE, MORE OF, LESS OF, PART OF, MORE THAN, OTHER THAN, to prompt the team to explore, systematically and in depth, possible deviations from the planned pattern of operation, to assess their consequences and to consider what needs to be done to deal with the hazards that are uncovered. Each step of the study is recorded in tabular form as it progresses. For each GUIDEWORD, each possible departure from operating intentions uncovered by the application of a guideword is recorded under DEVIATION, then the CAUSE of the deviation and its possible CONSEQUENCES and finally ACTION to be taken. The action might be, for example, a measure to be taken to eliminate the hazard, a search for more and better information or no action if the consequences are considered not to be detrimental. The technique is based on the assumption that incidents arise not because of a lack of knowledge or experience but because of the complexity of designs, needing systematic but imaginative analysis to uncover the hazards.

6.17 Although the release of genetically engineered organisms is a different activity in many respects from that of operating a chemical plant, we thought it possible that the HAZOP methodology might be applicable in the biological context and, with the enthusiastic support of scientists involved in genetic engineering, decided to set up a small working party to explore the feasibility. The names of those who took part are listed in Appendix 6.

6.18 The working party concluded that it would be difficult to apply HAZOP to the release of GEOs and devised a variation which, to avoid confusion, we have called GENHAZ. GENHAZ has not yet been fully worked out and tested. All those who have taken part in the work so far, however, have concluded that a fully developed GENHAZ would help to identify environmental impacts which might otherwise be overlooked. We have therefore made arrangements to continue the development and testing of GENHAZ to the stage at which a handbook can be made available, containing a detailed explanation and exemplification of the procedure, which will enable any organisation planning a release to undertake a GENHAZ study.

6.19 For a major new chemical plant, a HAZOP study may take several weeks whereas for a minor modification a single meeting may suffice. GENHAZ studies for proposed releases with similarities to previous releases are likely to be relatively quick, while those for proposed releases that have no precedent, are complex or pose serious environmental risks, are likely to require a greater commitment. We consider that a commitment to the application of a procedure which fulfils the objectives of HAZOP, if it could be devised, could contribute to the reduction of risk and to the reassurance of the public. As has been the case with HAZOP, we would expect benefits to accrue also in the recognition, at an early stage of the planning, of potential operational problems in addition to those that give rise to questions of safety, with consequent improvements in implementation.

6.20 It is important to remember, however, that HAZOP – and therefore GENHAZ – can only provide a part of the picture. It draws attention to the unforeseen. It cannot provide answers to factual questions about the

probability of events happening, for example the extent to which gene transfer mechanisms observed in the laboratory operate in nature. The chemical industry has a separate technique, known as HAZAN (hazard analysis), to address such questions. We discuss in Chapter 10 research needed to help to provide answers to these questions in relation to the release of GEOs.

Microcosms

6.21 Creating artificial environments, known as microcosms, where a genetically engineered organism's behaviour can be examined before release could be a useful way of reducing risks to the environment([83]). One type of microcosm can be in the form of a sample from the natural environment, such as a field or a lake, which has been brought into a greenhouse, growth chamber or laboratory tank. This aims to create conditions which are environmentally as realistic as possible within the confines of a controlled experiment. Alternatively, a microcosm can be artificially constructed consisting, for example, of sterile soil or distilled water, in order to test a particular aspect of an organism's behaviour.

6.22 Microcosms have been used extensively to test the likely impact of chemicals on the environment, forming a stage between laboratory testing and field trials. In genetic engineering, they could be useful for measuring the genetic stability of GEOs, gene transfer potential, the effects of specific environmental parameters on gene expression, the ability of GEOs to survive and the potential adverse effects of GEOs on the environment. For a variety of reasons related to the design and management of microcosms, however, it can be difficult to relate the results from microcosm experiments to the behaviour of organisms in the environment([84]). In addition, it may be difficult to use microcosms to investigate the environmental behaviour of birds or large animals and plants whose natural habitats cover large areas of land or sea with complex food webs. Research is needed on these issues to enable microcosms to fulfil their full potential for reducing the risks associated with release.

Step-by-step

6.23 Risks can be further reduced by ensuring that the uncertainties introduced at each stage of development of new organisms are limited. This operates on two levels. First, the progression from laboratory to widespread release should go through a series of stages gradually relaxing the degree of containment at each, for example from laboratory, to greenhouse, to single field trial, to wider trials, to full marketing([78]). As products move through these stages, responsibility for scrutiny may fall progressively to various bodies. For example, the ACGM will have oversight of contained laboratory work. Its Intentional Introduction Sub-Committee (paragraph 7.8) will assess field trials and other releases and, in so doing, may overlap with a product control or other authority looking at releases which are subject to particular statutory controls. Close links are needed between these various assessment bodies together with arrangements for exchange of information about assessments and about the results of releases that have taken place.

6.24 Secondly, there should be a step-by-step approach to innovation in the releases that take place so that the modifications made at each step do not introduce an unacceptable degree of uncertainty. The Institute of Virology's baculovirus release, described in Appendix 5 paragraphs 2–17, provides an example of this approach. The first field trial used a virus which attacks caterpillars, modified only to contain a marker sequence enabling the virus's spread to be monitored. The next trial took the modification one step further

by debilitating the virus so that it was less able to survive in the environment. The next step was to add to the virus a gene whose expression could be monitored in caterpillars to test whether the crippling of the virus had affected its ability to express proteins. This is intended to lead eventually to the addition of a gene or genes to increase the virulence of the virus to caterpillars.

Limitation of survival

6.25 Any risks associated with a release would be much reduced if it were known that the probability of the released organisms surviving and replicating in the environment was very small. Many commercial varieties of crop plants and some farm animals are already subject to this limitation. Maize, for example, is no longer able to shed its seed. Some crops require fertilisers, irrigation or other protection or sustenance in order to compete successfully. Some farm animals, such as high performance poultry, are similarly dependent on man. Genetically engineered varieties of such plants or animals will frequently have similar characteristics.

DEBILITATION SYSTEMS

One way to make a genetically engineered organism less fit to survive in the environment would be to interfere with its metabolic pathways so that it was dependent for survival on an external supply of particular nutrients. These nutrients would be provided in the environment in which the GEO was intended to grow. Once the supply of nutrients was withdrawn, the organism should die. A disadvantage of this approach is that the debility may make the GEO less effective for its intended purpose. In addition, the organism may find sufficient of the nutrients occurring naturally in certain environments in which case strains debilitated in this way may be able to survive independently. There are many naturally occurring organisms, for example some soil bacteria and some human pathogens, which are nutritionally very fastidious yet are able to survive.

Another approach would be to engineer into the GEO a gene sequence, called a suicide gene, which was expressed when the organism had achieved its purpose and would kill it. For example, a GEO might be engineered to degrade a particular pollutant. It would be possible to introduce into the organism genes coding for substances toxic to itself and which had regulatory regions which allowed their expression only in the absence of the pollutant. As the concentration of the pollutant declined the toxin-producing genes would express the toxin killing the GEO. A number of variations on this idea are feasible, for example linking a gene whose function is essential to the survival of the organism to a regulatory region which functions only in the presence of the pollutant. Another procedure would be to introduce a gene for a toxic product which responds to small amounts of an externally provided inducer compound.

Many approaches to limiting the survival of GEOs in the environment are currently being investigated. Difficulties that remain to be overcome include the problem that, if the GEO is in a dormant state, it may not respond to inducers or inhibitors. Moreover, the processes of natural selection are likely to favour mutations or other changes which will render the debilitation systems ineffective. Another possibility is that a debilitation gene may become associated with genes which confer advantages to the organism. In this way, and particularly if the gene is crippling rather than fatal to the organism, it may spread unexpectedly through a population.

6.26 Methods of engineering debilitating mechanisms into organisms, particularly micro-organisms, are being investigated to minimise any risk of unwanted persistence in the environment. The box above describes some

approaches to this. The systems may not be totally effective, for reasons explained in the box, and there may be circumstances where debilitated GEOs would not be practicable because they would not survive long enough to perform their intended function. Debilitation may nevertheless often be useful to reduce risks associated with a release, particularly during experimental field trials when persistence may not be crucial to the research.

6.27 The use of techniques to debilitate organisms may encourage the use of organisms which are known to have the potential to harm the environment and which would not otherwise be used. If the crippling gene or trait were to be lost the organism could then cause damage. This risk would need to be assessed during the scrutiny process. We do not consider that it undermines the concept and we recommend that the use of debilitating mechanisms should always be considered when genetically engineered micro-organisms are proposed for release.

Clean-up

6.28 Confidence is increased if, having released the GEO, it is possible to destroy it or at least to limit its persistence. Hospitals and contained facilities which handle plants, animals or micro-organisms have developed many methods for decontamination. These can involve various combinations of isolation, chemical sterilisation, treatment by heat, light or pressurised steam and incineration. Paragraph 5.42 contains examples of circumstances where harmful naturally occurring organisms have been eradicated from the environment.

6.29 Trial releases of genetically engineered organisms which have taken place in this country and elsewhere have also incorporated arrangements to prevent spread of the organisms and to ensure their removal after the experiments were complete, as described in Appendix 5. The potato experiment by the AFRC Institute of Plant Science Research at Cambridge (Appendix 5 paragraphs 23–34) involved manual deflowering of the plants, weeding and digging up, followed by careful disposal (Plate 9). The experiment with caterpillar viruses by the NERC Institute of Virology (Appendix 5 paragraphs 2–17) involved netting of the area to prevent spread of the virus by insects and animals and chemical decontamination at the end (Plate 10). Although such methods may be practicable for highly restricted field trials of GEOs, they are unlikely to be practicable for wider releases. If an organism were to find a widespread favourable environment, it might prove virtually impossible to control, as with some of the exotics discussed in Chapter 4. We recommend therefore that the potential for clean-up and decontamination should always be considered but it would nevertheless be prudent to work on the assumption that, once released, it may not be possible totally to eradicate an organism, particularly a micro-organism, from the environment.

Monitoring

6.30 The importance of properly thought out monitoring procedures to accompany the release of GEOs cannot be overstressed. We use the term monitoring here to cover both the activity of checking that a release takes place in strict accordance with the terms of any approval covering the release and with any guidelines on good practice for handling releases, and also the activity of recording the outcome of the release. Both of these aspects need careful attention.

6.31 Releasers should be given clear advice by the Release Committee, both in general guidance on good practice and in specific comments on their

releases, about the manner in which releases should be carried out including arrangements for security, for monitoring, for clean-up and for dealing with contingencies. Compliance with these arrangements should be checked by appropriately trained inspectors with authority to take action where necessary (paragraph 8.21).

6.32 So far as the outcome of releases is concerned, there are several separate aspects that need monitoring. In the case of experimental releases, the releasers will of course be interested themselves in recording the outcome of their experiments. Their interests may, however, be relatively narrow in comparison with the wider public interest in the release of GEOs. At least until more knowledge is gained and confidence acquired about the behaviour of GEOs in the environment, we consider that releasers should be required to carry out monitoring. We also consider that there is a need for wider, more general monitoring which we discuss at paragraphs 6.39–6.43.

6.33 When assessing a proposal, the Release Committee should consider the extent, methods and arrangements for the monitoring that should be carried out by the releasers. This should include, in the immediate vicinity of the release and in locations downwind or downstream of the release site or on vehicle routes to or from the site:

- the spread of the GEO and any introduced genes;
- the environmental impacts of the release; and
- any unexpected ecological event.

The environmental impacts that warrant monitoring are likely to differ considerably from case to case. In general, however, any effects on related species; on pests, parasites or predators of the released organism; on the air, soil or water in or near the release site; and on subsequent activities on or near the site are likely to need monitoring.

6.34 The releaser should report the outcome of the monitoring to the Committee at the end of the experiment, or immediately in the case of any significant unexpected event. The monitoring should also normally continue after completion of the experiment for an appropriate period depending on the nature of the release, with agreed arrangements for reporting the outcome. It is important that the monitoring should be designed in such a way that it does not concentrate solely on the obvious but attempts also to pick up events which were not anticipated. It will never be possible to ensure that everything of this nature is covered and unreasonable requirements should not be imposed on the releaser. It is necessary, however, to ensure that a degree of imagination is applied in developing the monitoring arrangements.

6.35 Techniques to track the survival and spread of a genetically engineered organism in the environment are an essential element of monitoring and will be important for commercial products as well as for experimental releases. The use of unique genetic sequences that can be identified and followed is mentioned in Appendix 5 (for example, paragraphs 20 and 21) in this context. Some GEOs to be released may be uniquely identifiable as a result of the engineering they have undergone. Until more is known about the consequences of releasing GEOs, however, it may be desirable to insert uniquely identifiable marker sequences into all GEOs to be released([85]). Ideally, the marker should be stable and associated with the added genetic material so that the movement of that material in the environment may be tracked independently of the original GEO. This is particularly important for micro-organisms.

6.36 Markers which consist simply of an identifiable sequence of bases enable the GEO to be readily identified using specially prepared gene probes. Antibiotic resistance markers are also sometimes used. We comment on this practice in paragraph 4.11. Full characterisation of the gene sequence of introduced genes, as recommended in paragraph 5.41, will also aid identification.

6.37 Even with the use of markers, monitoring the spread of released GEOs and of their introduced genes may pose difficulties. Genetically engineered small animals, including birds, fish and insects, which are not subject to strict containment, could present problems by escaping, breeding with any wild relatives and spreading the genetically engineered trait. There is already concern over the spread of undesirable characteristics. For example trout escape from fish farms and mice and other small animals disappear from laboratories. Even such small and relatively immobile invertebrates as water snails can travel considerable distances between isolated ponds, perhaps assisted by other animals. Larger mammals, particularly if domesticated, should pose fewer problems.

6.38 Pollen seeds and spores can travel vast distances. In some releases of transgenic plants the flowering and fruiting parts have been routinely removed to eliminate the risk of spread of genes (paragraph 6.29). Micro-organisms also pose monitoring difficulties. For example, it is estimated that at present fewer than 10% of species of soil micro-organisms can be cultured in the laboratory([8]). It can also be difficult to determine whether micro-organisms are dead or merely dormant and very little is known about fluctuations in the size of populations of naturally occurring micro-organisms.

6.39 General monitoring of the environment, as distinct from monitoring of particular releases, can also be useful in detecting or testing for unexpected changes. There is already a good deal of such monitoring taking place in the UK. As well as the work carried out by various public bodies, the country is fortunate in having many interested individuals and organisations through whose enthusiasm and dedication biological records have been built up over many years. The discovery of the environmental effects of DDT, leading eventually to its banning, is attributed to amateur ornithologists who noticed the decline in populations of peregrine falcons and other birds of prey. Evidence that the decline was due to the thinning of the shells of their eggs, and the correlation of egg-shell thinning with the use of DDT, was obtained by examining museum eggs, themselves generally collected in earlier years by amateur enthusiasts (an activity which, incidentally, would now for the best of reasons be illegal).

6.40 The Biological Records Centre (BRC) at the Institute of Terrestrial Ecology (ITE) was set up in 1964 after the Botanical Society of the British Isles had completed its first national survey of flowering plants. The BRC brings together data on animal and plant species supplied by about 60 different groups, most of them voluntary, and many individuals, who record the presence or absence of a species on site record cards. Recently people have been encouraged to give details about weather conditions and the nature of the locality, as well as the grid reference and date, when they record a sighting. The bigger botanical, ornithological and entomological societies submit the results of systematic surveys based on the 1km square grid for entry on the database which at present contains about 4 million entries. The data are to some extent geographically biased, mainly because of the greater concentration of voluntary participants in the more densely populated parts of the country. There are, for example, more data from SE England than from

elsewhere. The BRC data are available to the public and to researchers and are presented both in the form of species atlases and detailed records.

6.41 The BRC co-operates closely with the NCC, which concentrates on monitoring species of conservation importance but also has an interest in the general state of the natural environment. Pesticide residues have been monitored in birds of prey and in herons since 1963. This work is done by ITE for the NCC. It would be valuable if there were a close link between the BRC and the MAFF Wildlife Incident Data Base (WIDB) which is concerned with analysing the cause of death of wildlife in reported incidents. The MAFF is also concerned with the monitoring of pest and nuisance species as well as species of economic importance, such as game animals, bees and domestic pets.

6.42 We consider that there is scope for co-ordinating monitoring activities, building where appropriate on the work of voluntary organisations and the bodies referred to above, to develop a systematic approach to monitoring the health of the environment, concentrating perhaps on a relatively small set of particular species of animals and plants which might be identified as indicators for the purpose. We consider that the DOE should take the lead in promoting and funding this co-ordination work as part of its responsibilities for the protection of the environment.

6.43 Environmental monitoring is an essential part of the process of ensuring that no unacceptable or unexpected consequences arise from the release of genetically engineered organisms. We underestimate neither the difficulties nor the cost but we emphasise its importance. Financial returns may not be immediately obvious but in the long run it will be money well spent.

Review

6.44 A major cause for concern and of expense in the release of genetically engineered organisms is uncertainty as to the effect of a genetic modification on an organism and as to the impact of the resultant GEO on organisms, ecosystems and the environment at large. Experience of releases will reduce this uncertainty, even though perplexing new problems will undoubtedly emerge. The interests of environmental protection will be best served by making acquired experience available on an international basis to those who have the responsibility for advising on releases.

6.45 Certain results from release experiments may be commercially valuable and releasers may legitimately wish to protect these from wider exposure. We consider it important, however, that information which has a bearing on environmental safety, whether the implications are positive or negative, should be passed to the Release Committee. We consider that the Committee should identify at the outset certain categories of information which it will expect to receive on completion of or possibly even during the experiment. This will of course relate closely to its monitoring requirements.

6.46 The Release Committee should carry out regular reviews of the information it has obtained about the outcome of releases. This will help to ensure that any lessons are fed back into the assessment of new release proposals. Consideration should be given to publishing the results of the reviews where they were felt to contain points of wider public interest, subject to the need to protect any commercially sensitive material.

6.47 International exchanges of information between assessment bodies could also provide valuable material to assist in assessing release proposals.

The European Commission has proposed regular exchanges of information on this subject between member states([86]). We support this initiative. The OECD has proposed the development of an international database of releases. The European Commission is co-operating with this. An international store of information of this nature would be of immense value in the early years of release activity, both for research and to help establish whether any environmental problems may be associated with the release of a genetically engineered organism.

CHAPTER 7

THE PRESENT FRAMEWORK OF REGULATION

Introduction

7.1 The deliberate release of genetically engineered organisms into the environment is covered in the UK by a number of statutory and non-statutory arrangements, depending on the means by which the organism was produced and the purpose for which it is to be used. Reference is made later in this chapter to legislation which has been devised for other purposes but which applies in varying degrees to GEOs. First, however, we sketch the development of controls devised specifically in respect of GEOs.

The voluntary approach

7.2 Public interest in the potential hazards associated with genetic engineering was first focused by a letter from Professor Paul Berg of Stanford University, California, and ten other distinguished scientists, published in July 1974([64]), which called for a voluntary worldwide moratorium on the genetic manipulation of certain micro-organisms because of the possible danger to human health. In response to the public interest aroused by this in the UK, the Advisory Board to the Research Councils established a Working Party 'to assess the potential benefits and potential hazards of techniques which allow the experimental manipulation of the genetic composition of micro-organisms'. The Working Party was chaired by Lord Ashby, the first Chairman of the Royal Commission on Environmental Pollution. Its Report in 1975([65]) recommended that, 'because of the great benefits to which they may lead', such techniques should continue to be used, but subject to rigorous safeguards and under conditions of appropriate containment. In the same year a Working Party chaired by Sir George Godber published its Report 'The Laboratory Use of Dangerous Pathogens'([110]).

7.3 The Secretary of State for Education and Science then established a Working Party, under the chairmanship of Professor Sir Robert Williams, primarily 'to draft a central code of practice and to make recommendations for the establishment of a central advisory service for laboratories using the techniques available for genetic manipulation'. This they did in their Report in 1976([66]). The advisory body recommended was established in 1976 as the Genetic Manipulation Advisory Group (GMAG), with terms of reference including 'to advise those undertaking activities in genetic manipulation ... to undertake a continuing assessment of risks and precautions ... and to advise on appropriate action'. In addition to Reports, GMAG produced a series of Notes including guidelines for the categorisation of experiments([67]) and a code of practice for containment facilities([111]).

Health and Safety at Work Act

7.4 The need for regulation was initially perceived in the context of contained work in the laboratory and in small scale contained industrial applications. Powers under the Health and Safety at Work, etc. Act 1974 were used for the protection of those engaged in that work and to protect the wider public against risks arising from work activities. The Act (see the box opposite) empowers the Secretary of State, normally the Secretary of State for Employment, to make regulations on the advice of the Health and Safety Commission (HSC). In 1978 the Health and Safety (Genetic Manipulation)

Regulations were made, in this case by the Secretary of State for Education and Science. They require the notification to the Health and Safety Executive (HSE) of an intention to carry out genetic manipulation. The Regulations did not relate to the possible release of genetically engineered organisms into the environment, which was not then under consideration.

HEALTH AND SAFETY AT WORK, ETC. ACT 1974

The Act imposes a general duty on every employer 'to ensure, so far as is reasonably practicable, the health, safety and welfare at work of all his employees'; and a duty 'to conduct his undertaking in such a way as to ensure, so far as is reasonably practicable, that persons not in his employment who may be affected thereby are not thereby exposed to risks to their health or safety'.

The Act sets up two statutory bodies, the Health and Safety Commission (HSC) and the Health and Safety Executive (HSE). The HSE's functions are to exercise powers on behalf of the HSC and to enforce the Act. The HSC is empowered, amongst other things, to set up advisory committees, commission research, direct the HSE to carry out investigations and inquiries, advise the Secretary of State to make health and safety regulations, approve codes of practice and require the submission of information subject to safeguards on disclosure. The HSE is empowered to appoint inspectors with wide powers including the power to serve improvement notices and prohibition notices. The employer may appeal against these to an industrial tribunal.

The Secretary of State may make regulations covering, amongst other things:

- regulation or prohibition of manufacture, supply, use, transportation or import of substances, plant or processes as prescribed in the regulations;
- registration of people or premises;
- restriction of specified activities to specified people;
- monitoring of working conditions;
- imposition of conditions and requirements;
- requirement to obtain the approval of the HSC or other specified body;
- requirement to notify specified matters to specified persons;
- provision for exemptions from any of the provisions.

7.5 HSE inspectors have power under the Health and Safety at Work Act to serve an improvement notice or a prohibition notice in respect of any work activity. HSE have advised us that this could, in appropriate circumstances, extend to a deliberate release of genetically engineered organisms to the environment. Because their powers derive from the Health and Safety at Work Act, however, they may be exercised only to prevent harm to human health or safety, not to prevent damage to the natural environment.

Advisory Committee on Genetic Manipulation

7.6 In 1984 the HSC established an Advisory Committee on Genetic Manipulation (ACGM), replacing the GMAG, to advise the Commission and Executive, and health, agriculture, environment, industry and Northern Ireland Ministers, on several aspects of genetic manipulation, including: the general standards of safe working to be observed; the specific precautions necessary in individual cases of experimental work; and the nature of any

controls to be applied generally to laboratories and other workplaces engaged in genetic manipulation or the use of products of genetic manipulation. In addition to the Chairman, the ACGM contains 5 representatives of employers and 5 of employees, as well as 8 members chosen for their specialist knowledge. This reflects the emphasis of the Health and Safety at Work Act on worker health and safety. Government departments with an interest in this area provide assessors. The Committee is largely concerned with contained experimental and industrial work involving GEOs. Its general approach contains the following elements:

- the establishment of a properly constituted genetic manipulation safety committee at each centre of genetic manipulation;
- the dissemination of guidance on procedures and risk assessment;
- the inspection of laboratories and advice on and enforcement of good practice.

The ACGM has, from the outset, also taken a close interest in the planned release of GEOs. Its approach to that includes, in addition to the above:

- the establishment of a central, expert advisory committee to assess release proposals, with an expert secretariat and membership covering relevant scientific disciplines and public interests;
- the development of assessment criteria and policies on acceptable arrangements for release.

7.7 The ACGM established a working group to produce guidelines for the release of genetically manipulated organisms into the environment. This included departmental representatives and scientific experts, including some members of the main Committee. The working group later became the Planned Release Sub-Committee of the ACGM. The guidelines were issued with the approval of the HSC in April 1986. They recommend that:

- the HSE should be notified of any proposal to release GEOs;
- the notifier, when making his initial assessment of the environmental consequences of a release, should be advised by an appropriately constituted local body including relevant scientific expertise and, where appropriate, a local environmental health officer; and
- a case by case examination of proposals should be carried out on behalf of the HSC on the basis of risk assessment material provided by the proposer in accordance with the guidelines.

These arrangements have been implemented by the HSE largely on a voluntary basis but the HSC has submitted proposals for new Genetic Manipulation Regulations which will put them onto a statutory footing(7). They are expected to come into effect in 1989. Those proposing to release genetically manipulated or certain other organisms (see definition 4 in the box on page 9) will now be required to notify the HSE 90 days in advance with details of the proposed release, including the results of a risk assessment carried out locally.

7.8 Shortly after the issue of the guidelines, the ACGM established the Planned Release Sub-Committee to advise on the need for revision of the guidelines in the light of experience; and to consider individual proposals for release with respect not only to human health but also to animal and plant health and the environment in general, with particular reference to consideration of genetic manipulation aspects. The Sub-Committee, which is at present

chaired by Professor J E Beringer of Bristol University, contains representatives of the DOE, MAFF, Department of Health, Nature Conservancy Council and Natural Environment Research Council as well as scientists engaged in genetic engineering and other experts with appropriate knowledge. Its name was recently changed to the Intentional Introduction Sub-Committee.

7.9 The Sub-Committee had, at the end of March 1989, assessed 12 proposals for release and was handling about 5 cases a year. Each is considered in detail. Cases so far considered have concerned proposed experimental releases designed to acquire information for further research and development. They have enabled the ACGM to develop recommended procedures for risk assessment, for consultation arrangements and for monitoring. In all cases the Sub-Committee has acted unanimously. To date one proposal has been refused and others have been modified to meet the views of the Sub-Committee. Despite the voluntary nature of the arrangements, no release is known to have taken place without prior notification to, and the endorsement of, the Sub-Committee.

Other relevant legislation

Product controls

7.10 The Food and Environment Protection Act 1985 empowers Ministers* to make regulations controlling the import, sale, storage, use and advertisement of pesticides. They are advised in the exercise of their functions by the Advisory Committee on Pesticides, itself established by Regulations made under that Act. The Committee's secretariat is provided by the MAFF and the HSE. The controls apply to 'any substance, preparation or organism prepared or used for destroying any pest and to other substances, preparations and organisms as defined'. They are to be exercised with a view to the protection of the health of human beings, creatures and plants and the safeguarding of the environment. The Act does not refer specifically to genetically engineered organisms but it appears that they are covered. Regulations made under the Act in 1986 require a permit to be obtained not only for the sale or supply of a pesticide as a product but also for field trials. Exemptions exist for certain categories of field trial but these exemptions do not apply to trials of genetically manipulated organisms, all of which require a permit. Ministers have also decided to require applicants in respect of genetically manipulated pesticides to obtain the ACGM's approval before a permit under the pesticide provisions will be granted. These are important existing safeguards in an area of significant development for genetic engineering.

7.11 The Medicines Act 1968 requires most medicinal products to be licensed before sale or supply. The legislation covers, amongst other matters: conditions for authorisations; requirements for tests and trials; manufacture and wholesale of products; and labelling and packaging. Veterinary medicines and medicated animal feeding stuffs are also controlled through the licensing and certification provisions of the Medicines Act. The Act establishes the Medicines Commission to advise Ministers responsible for health and for agriculture on the exercise of their powers, and provides for the Ministers to appoint committees on particular topics; one such is the Committee on the Safety of Medicines, another the Veterinary Products Committee. The latter, in its assessment of the safety of veterinary medicines, takes into account the fate of the medicine and its metabolites in the environment.

* These are the Minister of Agriculture, Fisheries and Food; the Secretaries of State for the Environment, for Health, for Employment, for Scotland and for Wales; and the Northern Ireland Office.

7.12 Food and food additives are not subject to product licensing and certification controls. The Food Acts do, however, provide that Ministers may prohibit or regulate the use of any substance in any food intended for human consumption and of any product or treatment in the preparation of any such food. Additives in both food and animal feeds are controlled through EC Directives which allow the use only of substances appearing on a list.

7.13 The above mentioned product controls, and others, were not designed specifically to cover genetically engineered organisms used as or in products. In most cases their scope seems sufficiently broad to encompass such products although their use for that purpose is not beyond the possibility of challenge in the courts. Some products, however, are subject to no legislative control.

Control of plant, animal and human pathogens

7.14 The Plant Health (Great Britain) Order 1987, promulgated under the Plant Health Act 1967, contains prohibitions on the keeping, selling, planting, release, delivery or disposal of genetically manipulated material except under a licence granted by the Minister of Agriculture, Fisheries and Food. For the purposes of the Order, 'genetically manipulated material' is defined by reference to activities involving or producing or altering plant pests including pathogens. The Tree Pests (Great Britain) Order 1980 and the Import and Export of Trees, Wood and Bark (Health) (Great Britain) Order 1980 are also promulgated under the Plant Health Act and contain similar references to genetic manipulation and genetically manipulated material in the context of tree pests.

7.15 The Importation of Animal Pathogens Order of 1980, made under legislation now consolidated in the Animal Health Act 1981, regulates the importation of animal pathogens or of tissue which might carry pathogens. Outbreaks of serious disease amongst animals are notifiable under the Act, with provision for the slaughter of herds and the disinfection of any laboratory or other source of infection.

7.16 The Public Health (Control of Diseases) Act requires the notification to the Department of Health (DH) of work on certain human diseases. Any research or diagnostic work on dangerous human pathogens must be notified to the DH. Anybody intending to keep or handle certain listed pathogens, or to transfer them from one establishment to another, must notify the HSE under the Health and Safety (Dangerous Pathogens) Regulations 1981, made under the Health and Safety at Work Act. Other Regulations made under that Act require notification by the quickest practicable means to the HSE of the uncontrolled or accidental release or the escape of any substance or pathogen which might cause death, damage to health or injury to any person.

Transgenic animals

7.17 The Animals (Scientific Procedures) Act 1986, administered by the Home Office, regulates 'any experimental or other scientific procedure applied to a protected animal which may have the effect of causing that animal pain, suffering, distress or lasting harm'. The Act applies specifically to 'anything done for the purpose of, or liable to result in, the birth or hatching' of such an animal and hence to the application of genetic engineering techniques to a wide range of animals. Breeding from transgenic animals is regarded as a regulated procedure requiring licence authority until it can be demonstrated that the progeny are not likely to suffer adverse effects. The release of a transgenic animal into the environment would be regarded as removing it from a regulated procedure; release could not, therefore, legally be carried out until the Home Office was satisfied as to the animal's welfare.

The HSC has recently published guidelines([68]) for work with transgenic animals covering not only aspects of animal welfare but also the precautions needed to ensure the safety of the operator and other humans, animals and the environment.

Wildlife and Countryside Act

7.18 It has been suggested to us by the DOE([137]) that powers in the Wildlife and Countryside Act 1981 could in principle be used to control the release of certain types of genetically engineered organism to the environment. The Act regulates the release into the wild of animals which are not ordinarily resident in, or regular visitors to, Great Britain and the planting or otherwise causing to grow in the wild of scheduled foreign plants. The use of this Act to control the release of GEOs appears, however, to strain both the purpose and the interpretation of the legislation.

7.19 The DOE has recently established an Interim Advisory Committee on Introductions, under the Chairmanship of Sir Kenneth Blaxter, to advise the Department on the ecological implications of releasing novel organisms and viruses (other than those already covered by existing product controls) and to provide ecological advice to the HSE, ACGM and other departments and Government agencies on request.

The marine environment

7.20 Under Part II of the Food and Environment Protection Act 1985, a licence is required from the Minister responsible for fisheries to deposit any substance or article in the sea. In considering applications, the Minister must have regard to the need to protect the marine environment, the living resources which it supports and human health. The MAFF has advised us that the term 'substance' in this Act covers living organisms including, by implication, any which have been genetically engineered([131]).

Liability for damage

7.21 Part I of the Consumer Protection Act 1987 makes provision for liability for damage caused by defective products. Genetically engineered organisms used as or in products are not referred to explicitly but there appears to be nothing in the Act which would prevent a GEO being regarded as a product for the purposes of the Act. The Act enables a person who suffers personal injury, or in certain circumstances damage to property, caused by a product, to bring an action against the producer or importer of the product. There are, however, certain defences available against such an action including the state of scientific and technical knowledge at the time. It is doubtful whether an action could be brought under the Act for damage to wild animals or plants or to common land.

7.22 The common law is not likely to operate preventively in this context but, if damage does occur, aggrieved parties may attempt to bring common law actions based on negligence, nuisance or the doctrine expressed in the case of *Rylands v. Fletcher*([112]). In the *Rylands* case it was held that 'a person who for his own purposes brings on his land and collects and keeps there anything likely to do mischief if it escapes must keep it in at his peril, and, if he does not do so, is *prima facie* answerable for all the damage which is the natural consequence of its escape'. The doctrine, which creates a form of strict liability, as distinct from liability for negligence, appears to be aimed at accidental release and it is uncertain whether the courts would regard it as being applicable to the deliberate release of genetically engineered organisms. In any event, plaintiffs may have difficulty in proving a causal link between their loss and a release of GEOs, though developments such as the use of markers (paragraph 6.36) may be of assistance in this.

Strengths and weaknesses of the present framework

7.23 There is a substantial number of legislative measures which could, in principle, be used to control the release of genetically engineered organisms to the environment. Most were designed primarily to control the sale or supply and use of products though they may be, and in some cases are, used also to control trial releases for the development of products (for example pesticides). Few of these measures make any explicit reference to GEOs, however, many having been brought into force before genetic engineering techniques became available, and in some cases there may be doubt whether they could be used to control the release of GEOs. Each is limited in the range of organisms to which it applies and even taken together the measures do not appear to apply to all organisms. There is a clear need for fresh legislation to provide specifically for the control of releases of all categories of genetically engineered organism.

7.24 The guidelines issued by the ACGM for voluntary notification of releases, which are expected very shortly to be given statutory backing, go some way towards providing a basis for the assessment and control of releases of genetically engineered organisms in a consistent and co-ordinated manner. The Health and Safety at Work Act cannot, however, be used to control releases which present risk to the natural environment but which do not affect human health or safety. For this a separate and new power will be required. In the next chapter we set out the controls which we believe are needed to regulate deliberate releases of genetically engineered organisms.

CHAPTER 8

A PROPOSED STATUTORY FRAMEWORK FOR CONTROL

Introduction

8.1 Advances in genetic engineering techniques and concern for the environment lead us to conclude that statutory control of releases of genetically engineered organisms to the environment must be put in place. The Secretary of State for the Environment* should take primary responsibility for control with respect to the environmental consequences of such releases.

8.2 This chapter sets out the principles which we consider should underlie the statutory provisions. It also describes the means by which joint responsibility should be established between the Secretary of State for the Environment and the Secretary of State for Employment; the latter's responsibilities encompass the health and safety of workers involved in genetic engineering and of other people who may be directly affected by their activities. The chapter also indicates how full advantage should be taken of the successful operation to date of the Advisory Committee on Genetic Manipulation (ACGM) and its Intentional Introduction Sub-Committee. We seek to achieve an evolution of existing arrangements to accommodate changing needs.

A new statutory power

8.3 Any new statutory controls must complement the provisions of the Health and Safety at Work Act, described in Chapter 7, which constitute the statutory authority of the Health and Safety Commission (HSC) and therefore relate directly to the functions of the ACGM. They must also be consistent with product controls exercised by agriculture and other Ministers, also described in Chapter 7.

8.4 There is no clear dividing line between contained work and release to the environment. Rather, there is a continuum from secure containment in a laboratory, through stages including greenhouses and small scale trials, to general release of a product. At all stages there may be both environmental and human health issues to take into account. Where work is in contained facilities, the main regulatory concern is for the health and safety of the workforce, since the facilities are designed to prevent release to the environment (but see paragraph 8.29). For other work, provided the organisms are considered to pose little or no risk to human health or safety, environmental issues are more prominent. Continued scrutiny for any health and safety consequences remains necessary, however, and it is therefore essential that both the Secretary of State for the Environment and the HSC (acting on behalf of the Secretary of State for Employment) should be involved in decisions on release. This will ensure that the HSC, which is responsible for regulating the early stages of the development of a GEO in this country, is able to bring the knowledge it has acquired to bear on the question of release of that organism to the environment.

8.5 The control of releases of genetically engineered organisms should be governed by a statute establishing controls in respect of environmental

* Here and throughout this chapter, references to the Secretary of State for the Environment and to DOE should be taken as applying also to their territorial equivalents in Wales, Scotland and Northern Ireland.

protection and providing a framework within which the Secretary of State would be empowered to make regulations including a system for licensing. We foresee that such regulations would require amendment from time to time to keep pace with advances in technology and the development of knowledge and experience. The statute should, in addition, impose a duty of care obliging all those responsible for the release of a GEO, whether for experimental or commercial purposes, to take all reasonable steps for the protection not only of human health and safety but also of the environment.

A release licence

8.6 We have argued in Chapter 6 that, until experience justifies a relaxation, every proposal for the release of a genetically engineered organism must be subject to assessment by a national body of experts. A licence, which we refer to as a release licence, should be required before the release may take place. It should be an offence, carrying a substantial penalty, to release a GEO without having first obtained a release licence or to fail to comply with any conditions attached to the licence. For the reasons given in paragraph 8.4, we consider that any release licence should be granted by the Secretary of State for the Environment and the HSC acting jointly. We refer to them below as the licensing authorities. Anyone proposing that a GEO be released into the environment should therefore be required to notify the licensing authorities and to furnish them with details of the organism concerned and the method of release, including the results of an assessment of safety carried out by a local safety assessment committee. The licensing authorities should have the power to revoke the licence or to amend its terms if they had reason to believe that the continuation of the licence in its existing form was inadvisable.

8.7 The new Genetic Manipulation Regulations referred to in paragraph 7.7 are less stringent than this, requiring only that the HSE be notified of a proposal to release, with appropriate details, so that an assessment may be made and a decision taken as to whether it is necessary to intervene. We recommend that the new Regulations should be revised to provide that the HSC's approval to release be given in the form of a licence.

8.8 In the light of experience the licensing authorities may consider it to be safe to issue a release licence for a class or category of related GEOs; provision for this should be made in the legislation. Persons or organisations wishing to make releases under such a licence should, however, be required to submit their proposals to the licensing authorities who would decide whether they fell within the scope of that licence. The authorities should have the power to require that any proposal with features which gave rise to concern should be the subject of an application for a specific release licence, even though it appeared to be covered by a licence for a category.

8.9 A genetically engineered organism will probably pass through several stages of experimental development and trial release. Each stage of release should be the subject of a licence as described above. The organism may then be proposed for use as or in a product. As such it would often be released to the environment, either as part of its intended use or as a consequence of its disposal as a waste product. It should be assessed once more at that stage and be subject to licensing by the licensing authorities — that is, the Secretary of State for the Environment and the HSC acting jointly — for sale, supply or use as or in a particular product. If no other product control applies to that product the licence should be issued directly by them. Many such products, however, are subject to other controls, including those described in paragraphs 7.10–7.12. Where other product controls apply, the product control authority should be required to inform the licensing authorities of any

application for approval of a product which is or which contains a genetically engineered organism. They in response would inform the product control authority whether they were willing to issue a release licence for the product. This applies both to products developed in this country and to those imported. Anyone applying for approval to the sale or supply of a GEO as or in a product should therefore be required to state in the application that it is genetically engineered.

Additional powers

8.10 The Secretary of State for the Environment should be given additional powers including the power to:

- set up advisory committees (paragraph 8.11);
- draw up and publish codes of practice;
- maintain a register of people and organisations approved to carry out releases (paragraphs 8.17 and 8.18);
- make information available to the public and to other authorities (paragraphs 8.23–8.26);
- deal with emergencies and impose obligations on others to establish emergency arrangements;
- carry out or require others to carry out appropriate monitoring (paragraph 8.20);
- require the provision of information about releases;
- require the proper disposal of waste products and, if necessary, cleaning up of release sites (paragraph 8.29);
- inspect premises (paragraph 8.21);
- recover the costs of regulation.

The HSC already exercises many of these powers under the Health and Safety at Work Act. The Government should consider whether the Commission's powers need to be extended, in respect of the release of GEOs, to cover some or all of the remainder.

A Release Committee

8.11 The Secretary of State for the Environment and the HSC should refer each application for a release licence, or for product approval, in respect of a genetically engineered organism, to a committee of experts and should take account of its recommendations. The primary function of the committee should be the assessment of such proposals with regard to environmental protection and human health and safety. The present Intentional Introduction Sub-Committee of the ACGM makes such assessments. In our opinion the Sub-Committee is carrying out its functions effectively and is a sound basis from which to develop. The task which it performs is already distinct from that of the ACGM itself and will become more important as the number of releases grows. We therefore recommend that it should be constituted as a committee in its own right, distinct from the ACGM. It should be charged with giving advice to both the HSC and the Secretary of State for the Environment. We refer to it as the Release Committee.

8.12 The Release Committee should have close links with the ACGM. This may be achieved through common membership and a joint secretariat. Proposals for release which are the culmination of development projects carried out in this country may already have been considered by the ACGM whilst in the earlier phases of contained work. The knowledge thus gained by the ACGM and its secretariat will be of immense value to the Release Committee. We see advantage in one organisation acting on behalf of both the licensing authorities in the administration of handling applications, so as to provide a single point of contact for applicants; the HSE might be best fitted to do so.

8.13 Members of the Release Committee should have expert knowledge of genetic engineering techniques, microbiology, theoretical or field ecology or other relevant disciplines. They should be drawn from universities, other institutions, industry and workers' representatives. Persons engaged in the development and release of GEOs should not be debarred from membership of the Committee but interests should be declared appropriately. Experts from the UK and from other countries should be invited to join the Committee on an *ad hoc* basis when needed for the assessment of particular proposals. There should also be representation from relevant Government departments and agencies and from local authority environmental health officers. For instance, the input which the Nature Conservancy Council is able to make to the work of the present Sub-Committee, and which they will be able to make to the proposed Release Committee, is important.

8.14 The present Sub-Committee seeks the unanimous consent of its members before agreeing to a proposal for a release. Under our proposals the decision on a release will lie with the Secretary of State for the Environment and the HSC jointly and with other Ministers exercising product controls. It would not be appropriate for them to commit themselves in advance to refuse an application for release if any individual member of the Release Committee were opposed to it. They will be required to look at the merits of each proposal in the light of the best information available, including the advice of the Release Committee. If members of the Committee are not able to agree on a proposal they will need to consider what form of advice would be most helpful to Ministers and the HSC in reaching a decision on the application. In many cases a majority recommendation recording any dissenting opinion may be the best approach.

8.15 In addition to advising on proposals for release, including any conditions which should be attached to licences, the Release Committee should have other functions including:

- development of codes of practice and guidance for applicants;
- advising on the scope for categorising releases;
- advising on the need for research especially on matters relating to release;
- reviewing the outcomes of releases;
- liaising with overseas organisations in relevant fields; and
- advising on possible needs for changes in legislation or procedures.

The Committee should be asked to produce an annual report on its activities, on developments in the subject and on lessons learned. Adequate resources should be provided for its effective operation.

8.16 The DOE's Interim Advisory Committee on Introductions (IACI) which is described in paragraph 7.19 was, as its name suggests, established on an interim basis pending the recommendations in this Report. Our proposal is that the functions of the Committee should be taken on by the Release Committee, so that there will be no continuing need for IACI. Any necessary ecological expertise not available on the present ACGM Intentional Introduction Sub-Committee should be added to the Release Committee, or else provided to that Committee by other means, so that the Release Committee will be the Government's authoritative source of advice on questions pertaining to release.

Registration of releasers

8.17 In addition to the need for a release licence as described in paragraph 8.6, it is important that trial releases should be carried out under the supervision of competent persons. We recommend that the Secretary of State for the Environment and the HSC, acting on advice from the Release Committee, should compile and maintain a register of persons authorised to release GEOs. It would be an offence for a person not so registered to be responsible for carrying out a trial release. A registered person would be held personally responsible by the registration authorities for the use of appropriately qualified and trained staff for every aspect of the release and for the issuing of adequate instructions for them. He or she should be required to record the names of all staff engaged in the release and to make the names available to the registration authorities if requested. Appropriate arrangements should also be made for the registration of companies or other organisations which carry out trial releases. Criteria for their entry to the register should include the employment of suitably qualified personnel, the provision of appropriate training, designation of safety officers and the establishment of a local safety assessment committee. Registered organisations should be required to identify one or more registered persons who would be responsible for releases.

8.18 Registration, either of persons or of organisations, could be made in respect of a single release, a specified series of releases or any release of a specified class or classes of organism. The registered person or organisation carrying out the release would not necessarily be the same as the one who or which sought and obtained the release licence. In addition to trial releases, it might occasionally be appropriate to require the registration of releasers of a licensed product: for instance, if the product required particular precautions to be taken to ensure its safety but it offered benefits sufficient to justify its approval as a product. Provision for this should be made in the legislation.

Liability for damage

8.19 The present position with regard to liability for any damage arising as the result of a release of genetically engineered organisms, including the relevance of the Consumer Protection Act, is described in paragraphs 7.21 and 7.22. The new legislation should provide that, in addition, any person, or the directors of any company or other organisation, responsible for carrying out the release of a GEO without the necessary licence and registration, will be subject to strict liability for any damage arising. It should also provide that neither the licensing and registration authorities, nor members of the Committee on whose advice they or either of them acted in granting the licence or registration, should be liable in respect of the consequences of the release.

Monitoring and enforcement

8.20 The principal requirements for monitoring the effects of a release were described in paragraph 6.33. The Secretary of State for the Environment

should have the power to impose, in the release licence, a condition that the licence holder monitors the spread and fate of the organisms and of any introduced genes, the environmental impact of the release and any unexpected ecological event. The licence holder should be required to report the results of the monitoring to the licensing authorities, with immediate reporting of any significant untoward occurrence. Such monitoring will normally be needed only in respect of trial releases but there should be provision for it to be required also, on a temporary basis, in the case of licensed products where necessary.

8.21 The DOE and the HSE, and other departments where appropriate, will need to be able to check that the conditions of the release licence are complied with and that good practice is followed. The DOE should consider what in-house capacity it requires in this area but it will probably find it convenient for the most part to rely upon other bodies. One of these is HM Agricultural Inspectorate, part of the HSE. Adequate resources would have to be made available to the HSE for this task. The need for long-term general monitoring of the environment is described in paragraphs 6.39–6.43.

Public access to information

8.22 In previous Reports, notably the Tenth Report 'Tackling Pollution — Experience and Prospects'([108]), we have emphasised the importance of providing public access to environmental information, subject to the need to safeguard genuinely sensitive commercial information. That applies with particular force in this area. The potential benefits which we foresee are likely to arise from exploitation of genetic engineering could be frustrated by public opposition motivated by fear of the unknown. Relevant information relating to a proposed release of genetically engineered organisms to the environment should therefore be made available to the public before the release takes place. Further, this information must be open to examination and assessment by suitably qualified scientists and others who may be engaged by public interest bodies for the purpose. A field trial, as well as the sale or supply of a product, may give rise to concern, so there must be public access to information at several stages of development.

8.23 We recommend that there should be a public register of applications for release licences (paragraph 8.6) and of licences granted. This should contain the names and addresses of the persons or organisations making the applications, particulars of the organisms, the purposes of the releases and descriptions of the release sites. Since licences will be granted by the licensing authorities at national level, the register should be maintained nationally. Relevant sections of it should be kept in the localities of releases. Other information about releases, concerning foreseeable effects and arrangements for monitoring and dealing with emergencies, should be made available by the DOE or the HSE on request. The national register should contain, in addition, details of applications and licences granted for the sale or supply of GEOs as or in products (paragraph 8.9). The register of authorised releasers (paragraph 8.17) should also be made public.

8.24 Persons or organisations applying for licences to carry out trial releases of GEOs should be required to place advertisements, in the local press serving the areas of intended releases, announcing their proposals. The present ACGM Intentional Introduction Sub-Committee asks applicants to do this as a normal practice. Anyone applying for a licence for the sale or supply of a GEO as or in a product should be required to place a notice in the London Gazette and an advertisement in an appropriate national newspaper.

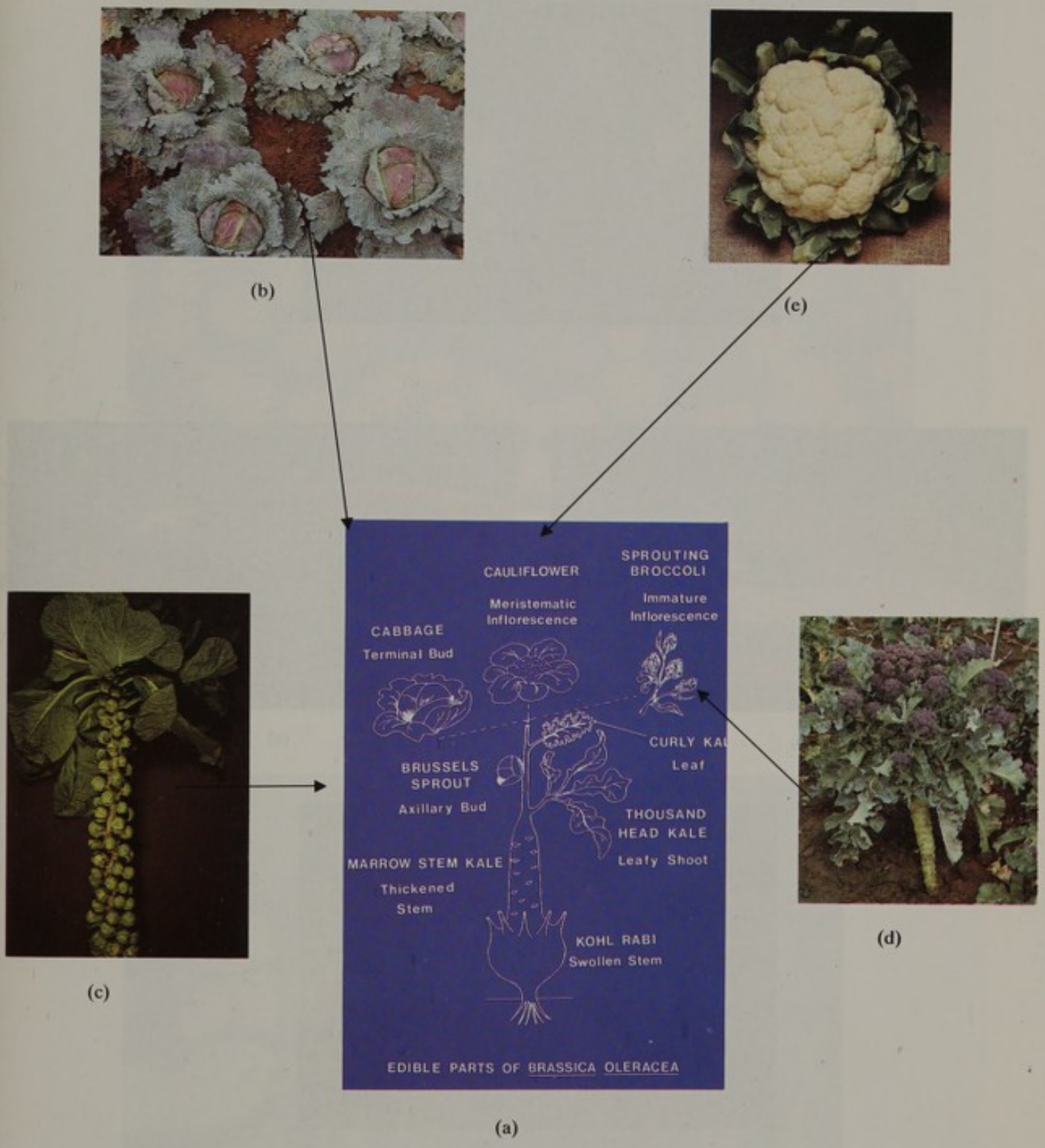


Plate 1 (a) *Brassica oleracea*; this plant has been bred in a number of ways to produce different, but related vegetable crops. Cabbage (b) and Brussels sprouts (c) are different types of leafy bud. Broccoli (d) and cauliflowers (e) are types of flowering head (paragraph 2.6).

Photograph by courtesy of the AFRC Institute of Horticultural Research, Wellesbourne (Dr. D.J. Ockendon and A.R. Gray).

(a.i) (a.ii)

(b)

(c)

(d)

Plate 2 Use of *Rhizobium* bacteria in rural Africa to improve plant growth. (a.i) Soya bean root showing nodules enabling it to fix nitrogen. (a.ii) Packet containing *Rhizobium* bacteria which live in the nodules. (b) *Rhizobium* in the form of a black powder. (c) Inoculating seeds with *Rhizobium* powder using a little water. (d) Soya beans on the left inoculated with *Rhizobium* are green and more vigorous than the yellowing, uninoculated plants on the right (paragraph 2.20).

Photograph by courtesy of the UN Food and Agriculture Organisation and the Rothamsted Experimental Station, Hertfordshire.

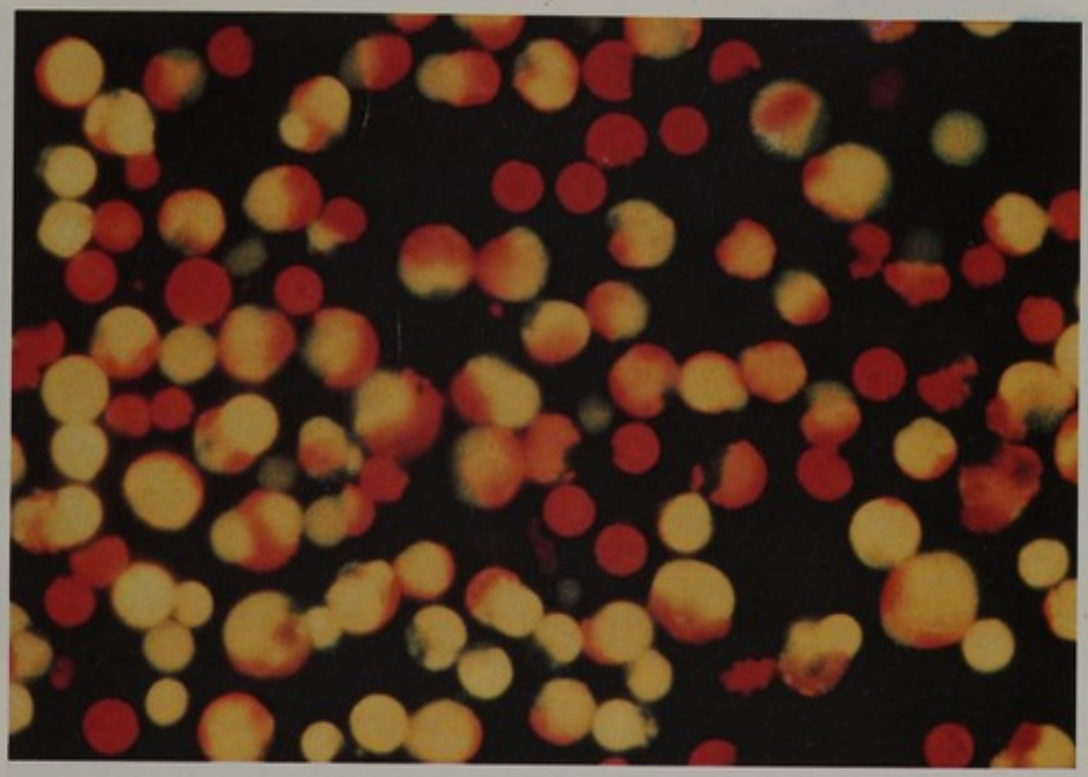


Plate 3 Cells produced by protoplast fusion viewed down a microscope. Fused protoplasts show red and yellow fluorescence; unfused cells are either only red or only yellow (paragraph 3.17).

Photograph by courtesy of the Department of Botany, University of Nottingham (Professor E.C. Cocking).

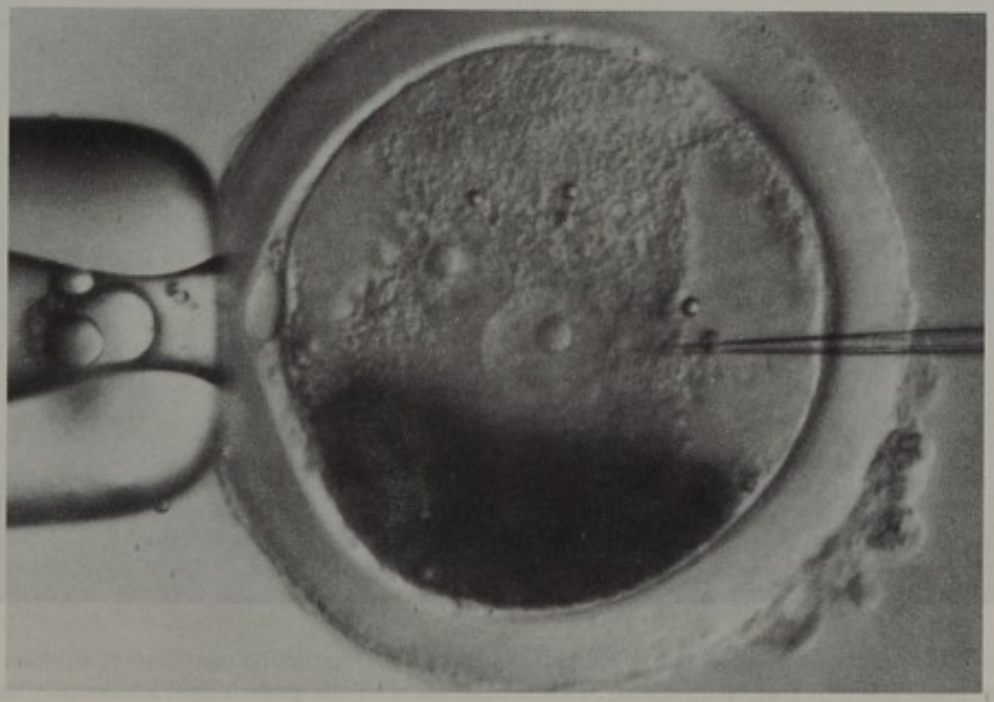


Plate 4 Micro-injection of DNA using a very thin syringe directly into the nucleus of the egg of a pig (paragraph 3.18).

Plate 5 Rhododendron plants spreading through Snowdonia National Park (paragraph 4.17).

Photograph by courtesy of the Snowdonia National Park Authority.

Plate 6 An elm hedge totally killed by Dutch elm disease, a virulent strain of a pathogenic fungus accidentally imported into this country in timber from America (paragraph 4.18).

Photograph by courtesy of Mr. A.J. Errington.

Plate 7 'In addition to landscape effects, oilseed rape plants that have colonised non-agricultural land, now represent a source of genetically mixed pollen which may impede efforts by the farming community to introduce improved strains of oilseed rape crop plants' (paragraph 4.26).

Photograph by courtesy of the Cambridge Photographers (B. and P. Seymore).

(a)

(b)

Plate 8 (a) A tobacco plant genetically engineered to protect it from the American caterpillar *Manduca sexta*; (b) a non-engineered plant (paragraph 2.24).

Photographs by courtesy of the Department of Biological Sciences, University of Durham (Dr. V. Hilder, Dr. Angharad, Dr. Gatehouse and Professor D. Boulter).

(a)

(b)

(c)

Plate 9 Field trials of transgenic potatoes at the Institute of Plant Science Research. (a) Transgenic potatoes being planted. (b) The potato plants have been deflowered to prevent the engineered genes being spread in pollen. (c) Transgenic potatoes harvested by hand to reduce the risk of transgenic tubers remaining in the ground (paragraph 6.29 and Appendix 5 paragraphs 23–34).

Photographs by courtesy of the AFRC Institute of Plant Science Research, Cambridge (Dr. P. Dale).

(a)

(b)

(c)

Plate 10 A field trial by the Institute of Virology of a genetically engineered virus which attacks caterpillars. (a) Cabbages exposed to caterpillars infected with the virus; (b) cabbages exposed to the uninfected caterpillars. (c) The field trial enclosure designed to exclude insects, small mammals and large mammals (paragraphs 4.3, 6.29 and Appendix 5 paragraphs 2–17).

Photographs by courtesy of the NERC Institute of Virology, Oxford (Professor D.H.L. Bishop).

8.25 The legislation should empower the licensing authorities to allow public access to information on the basis of which the Release Committee has made its recommendation. It should also enable them, if they considered it appropriate before allowing access, to invite the applicant to comment on the request for information and to take account of the applicant's views on commercial confidentiality. Those views will be coloured by the degree of legal protection afforded to the applicant's intellectual property (paragraphs 10.11–10.19). The arrangements we recommend represent a significantly greater degree of public access to information than is the case for pharmaceuticals and other products. We consider them to be justified by the likely high level of public interest in, and concern about, the release of genetically engineered organisms.

8.26 The licensing authorities will also need to be able to communicate information about release proposals to the European Commission and competent authorities in other EC member states and other countries, as described in the following chapter. If a specific power is necessary for that, it should be given to them. The information will often include commercially sensitive information which it would not be appropriate to make publicly available. The UK authorities should also, if necessary, be empowered to make information available to the OECD, UNEP and other international organisations, and should do so to the fullest extent possible.

An opportunity to comment

8.27 Members of the public should have the opportunity to make representations to the licensing authorities in respect of any application for a release licence within 30 days of the appearance of the local or national advertisement referred to in paragraph 8.24. The applicant, and anyone who has made such representations, should subsequently receive a copy of the recommendation made by the Release Committee and be given the opportunity to make representations about that recommendation before the decision of the licensing authorities is taken.

The marine environment

8.28 The legal basis of control for the release of organisms into the marine environment was described in paragraph 7.20. This appears not to provide the full range of controls which we consider to be necessary in the case of GEOs. We therefore recommend that the powers over the release of GEOs which are to be exercised by the Secretary of State for the Environment and the HSC should apply to the marine environment within UK territorial waters. They should exercise these powers in consultation with the Minister responsible for fisheries.

Waste disposal, storage, transport and import

8.29 In addition to the controls over planned release described in paragraphs 8.3–8.10, there will need to be an extension of controls over contained work on genetically engineered organisms to minimise the risk of damage to the environment. These will include powers to require the proper disposal of waste products and to regulate storage, transport and import for contained use. The powers should be given to the Ministers already having responsibilities in those areas. The Secretary of State for the Environment, for instance, should be given power in respect of waste disposal. In exercising his power, including the issue of advice by Her Majesty's Inspectorate of Pollution to the waste disposal authorities immediately responsible, he should receive advice from the ACGM and, as appropriate, from the Release Committee and elsewhere. The wide range of different types of GEO suggests that detailed guidelines will be required (see also paragraphs 10.9 and 10.10). Similar

considerations apply to the storage, transport and import of GEOs; some organisms present very little risk and may be handled by normal methods, whilst others will require special care. It would be helpful if the Secretary of State for the Environment were to draw the attention of his Ministerial colleagues and the HSC to the need to take full account of environmental issues involved in the handling and use of GEOs in their control over these matters.

Non-engineered organisms

8.30 Paragraph 5.49 described concerns which have arisen over the selection and use of naturally occurring organisms and the way in which these concerns are likely to become sharper over the next few years. We recommend that the Secretary of State for the Environment, together with agriculture and other Ministers, should conduct a review of these issues and should consider the possibility of enacting more comprehensive controls than those afforded by the Wildlife and Countryside Act and other present legislation. He could seek advice on the exercise of his present powers, and of any new power, from the Release Committee.

CHAPTER 9

INTERNATIONAL ASPECTS OF REGULATIONS

Introduction

9.1 Pollution can cross national boundaries; it is often subject to international regulations; and specific kinds of pollution are generated in similar circumstances in different countries. Variation between countries in the strictness of the control regime may influence the location of development activities and production. All these aspects of pollution problems are equally applicable to the deliberate release of genetically engineered organisms. Indeed, the relative simplicity of the technology, and the possibility that released GEOs may multiply and spread unexpectedly and uncontrollably, make international variation in control regimes a more serious problem in respect of genetic engineering than of some other areas of activity. Agreed international approaches to regulation of the release of GEOs, and to the exchange of information, are therefore particularly important.

9.2 In this chapter we first outline developments in the regulation of release of genetically engineered organisms in a number of other countries. We then consider the discussions in the Organisation for Economic Co-operation and Development (OECD) and comment in some detail on the European Community proposals. Finally we turn to the problems and opportunities posed by the application of genetic engineering techniques in developing countries.

Regulation in other countries

9.3 Many countries are considering the need to introduce specific legal controls over the deliberate release of genetically engineered organisms, though few as yet have legislation in place. Arrangements in a number of countries are described below but these are by no means the only ones in which progress is occurring. In addition many countries already have controls on specific classes of product, for instance as defined by use. These may be used to regulate the sale or supply of genetically engineered organisms as or in products.

Denmark

9.4 Denmark was the first country to enact comprehensive legislation designed specifically to regulate genetic engineering and the production, import and release of genetically engineered organisms. The main features of the Danish Environment and Gene Technology Act 1986 are([114]):

- restriction of genetic engineering research to classified laboratories (with power to make exemptions for educational purposes);
- prohibition on the deliberate release of genetically engineered organisms, though the Minister of the Environment may in special cases give an approval;
- requirement to obtain the approval of the Minister of the Environment for the production, sale, import or use of substances, foodstuffs, additives etc containing GEOs;
- power for the Minister of the Environment to make rules covering procedures for approvals, for storage and transportation and for disposal of waste; to impose terms and conditions on approvals; to

ask for information and to levy charges; to grant approvals which are limited in time and to change their terms; and to designate authorities (for example, local authorities) to supervise the implementation of decisions; and

- procedures for complaints and enforcement.

9.5 The Danish Act applies to deletions, self-cloning and most hybridisations and gives the Minister a general power to extend its application to other gene technologies. The Minister also has a power to exempt certain genetically engineered organisms from control under the Act under specified conditions. The Act states that its purpose is to protect the environment, nature and health, including considerations of nutrition, and that great weight is to be attached to the character and ecological condition of the environment as well as to the risk of an undesired effect. It was intended to be restrictive in approach and has indeed proved to be so. It is reported that some large Danish firms have decided to develop facilities elsewhere([113]).

West Germany

9.6 In the Federal Republic of Germany a Commission of Enquiry on 'Prospects and Risks of Genetic Engineering' has produced a comprehensive and detailed report([75]). It recommended:

- a ban on the release of genetically engineered viruses, except for human and animal vaccines and perhaps in due course baculoviruses;
- a moratorium of at least five years on the release of most genetically engineered micro-organisms whilst research into their safety is carried out;
- a requirement that the release of genetically engineered plants and animals be subject to approval by the Central Commission on Biological Safety on the basis of case by case assessment.

The Commission also recommended the introduction of legislation to regulate the whole area of genetic engineering.

9.7 The German Government is bringing forward legislation but we understand that there is some doubt as to whether the proposal for a moratorium is likely to be accepted. Already, however, there is an informal ban on releases, with exemptions considered on a case by case basis([6,115]). There is strong public opposition to proposed releases([115]). It is reported that some German companies are proposing to locate development facilities elsewhere, for example in the USA([116]).

Other West European countries

9.8 Elsewhere in Western Europe, countries are at various stages of development of regulation. The Netherlands have published draft regulations to be made under their Environmentally Hazardous Substances Act. These would require a permit to be obtained from the Minister for the Environment. Legislation is also expected in Sweden. The governments of several other countries, including France, Ireland and Greece, have established advisory committees to consider proposed releases of genetically engineered organisms but have not enacted specific legislation to control release.

The USA

9.9 The USA has introduced no new legislation to regulate the release of genetically engineered organisms but the White House Office of Science and

Technology Policy published in 1986 a 'Co-ordinated Framework for the Regulation of Biotechnology'([117]) which described the various regulations relevant to controlling releases, the policies of the authorities responsible for administering those regulations and the arrangements for co-ordination where jurisdictions overlapped. Many releases will be controlled through product legislation in areas such as pesticides, drugs and foods. For a release of micro-organisms, if no product legislation applies, the Toxic Substances Control Act (TOSCA), administered by the Environmental Protection Agency (EPA), is brought into play. Under this Act, the EPA is entitled to 90 days notice of manufacture or import of a new chemical substance or mixture including 'any organic or inorganic substance of a particular molecular identity'. The EPA argues that micro-organisms are chemical substances which are 'new' if they contain genetic material from different taxonomic genera. The Act gives the EPA powers to regulate chemical substances if it considers that they pose an 'unreasonable risk of injury to health or the environment'. In 1988 the EPA proposed new regulations under TOSCA([76]) which would require production for commercial research and development purposes of specified categories of micro-organism to be notified to them or, in some cases, to a local environmental bio-safety committee.

9.10 These arrangements have generated a degree of controversy within the USA. Biotechnology companies, researchers and others have criticised them for being fragmented with a variety of agencies involved — for example the National Institutes of Health, the Food and Drug Administration, the US Department of Agriculture and the EPA — who may not adopt consistent policies or criteria. There has also been comment about the validity of using TOSCA which was drawn up to regulate conventional chemicals([118]), about the conflicts of interest that might exist in some of the regulatory agencies which have responsibilities both for promoting research and for regulation([8]), and about the absence of regulatory oversight for certain types of GEO([119]).

9.11 The National Institutes of Health have recently been directed to establish a National Biotechnology Policy Board to review and appraise Government and other research activities in biotechnology. On the basis of that review the Board is to make recommendations on policies to enhance research and commercial application and to ensure that the regulatory system protects the public health, safety and environment without unduly impeding academic and commercial activities([120]).

Australia

9.12 The Federal Government in Australia has established a Genetic Manipulation Advisory Committee to operate voluntary controls based on the issuing of guidelines and a case by case assessment of proposals. A previous body, the Recombinant DNA Monitoring Committee, issued 'Procedures for Assessment of the Planned Release of Recombinant DNA Organisms', a substantial contribution to the literature on this topic([121]). Legislation to control releases is not proposed at present.

Canada

9.13 Canada has a wide-ranging Environmental Protection Act, proclaimed in June 1988, which controls all substances new to Canada either by manufacture or import. Separate parts of the Act deal with chemicals and biotechnology products including genetically engineered organisms. The manufacture (including production for research) or import of any substance not on a list of existing substances requires a permit from the Environment Minister of the Federal Government. The controls apply only to products which are not the subject of other controls. Biotechnology products being

developed for environmental application must be subject to field trials before commercial manufacture. Field trials must be approved in advance by the Environment and Health and Welfare Departments. Regulations under the Act, to provide detailed control of biotechnology products, are in preparation([122]).

Japan

9.14 In Japan several Ministries and Government agencies have issued guidelines on the contained use of genetically engineered organisms. The Science and Technology Agency has issued a 'Guideline for non-contained experiments of rDNA plants' and is preparing one on micro-organisms. The Ministry of Agriculture, Forestry and Fishery has issued a 'Guideline for using rDNA organisms in the field of agriculture, forestry and fishery'. The Environment Agency has established an Experts Group on Biotechnology and Environmental Protection to consider topics such as monitoring and evaluating the 'field utilisation of biotechnology' and to advise on environmental problems; an interim report was published recently([154]).

New Zealand

9.15 The New Zealand Government is reviewing its arrangements for controlling the release of GEOs and of new imported organisms, in the context of a wider review of legislation on environmental protection. It is expected that recommendations will be made in July 1989([123]).

The USSR

9.16 The USSR Committee on Recombinant DNA has adopted guidelines which cover, amongst other things, the release of GEOs to the environment. The guidelines, which are binding, require the submission of all proposals for release to the state authorities for approval([155]).

The Organisation for Economic Co-operation and Development (OECD)

9.17 The OECD has been active in developing guidelines for contained work and is now focusing on the issues surrounding release. During 1988 it set up working groups to look at various aspects of this subject including the problems of definition, public perception and safety assessment, which are discussed in earlier chapters of this Report. One group is developing the concept of Good Industrial Large Scale Practice; this was formalised in the OECD's 1986 report on 'Recombinant DNA Safety Considerations'([78]) and has been widely adopted for industrial applications of biotechnology. Another is looking into the feasibility of setting up a database of releases of genetically engineered organisms; we comment on this in paragraph 6.47.

9.18 The OECD has no regulatory authority, although it can establish procedures which its member states may agree to adopt. The impact of its discussions is primarily through the influence it has on policies in individual countries, thereby contributing towards consistent approaches to a problem. The OECD's work in this field to date has been highly respected and has been influential in member states and in other countries. The conclusion to the work on release will, we are sure, be equally influential. We therefore strongly support the activities of the OECD in this sphere and hope that the UK Government will continue to play a major and positive role.

The European Community

9.19 In April 1987 the European Commission (CEC) published proposals for Community-wide regulation of both contained work on and planned release of genetically manipulated organisms. In November 1988 draft

Directives were placed before the Environment Council for consideration([6,124]). As part of our study we had informative discussions with representatives of the CEC about their proposals, particularly in relation to releases.

9.20 The draft Directive on release is in two parts, one dealing with releases for experimental purposes, the other covering the placing of products onto the market. Definitions of genetic engineering and of release are included. It appeared from our discussions with CEC officials that they had encountered similar difficulties to our own (described in Chapter 2) in trying to arrive at suitable definitions and that they were receptive to proposals to improve them.

9.21 The draft Directive's proposals for regulation of experimental releases have many similarities to our own. Their main feature is a requirement for each release to obtain the 'endorsement' of an approving authority in the country in which the release is to take place. Without such endorsement the release cannot take place. This appears to allow for the explicit form of approval which we recommend for the UK (the release licence, paragraph 8.6) though it does not appear to require it.

9.22 The draft Directive requires that each proposal for an experimental release should be notified to other countries in the Community who would then have an opportunity to comment but not to prevent the release from proceeding. Experimental releases will normally be relatively small in scale and, if our recommendations for assessment and control are adopted, the risks of untoward events outside release sites should be minimised. Nevertheless, there may be circumstances where other countries have a legitimate environmental interest in the proposal. The release site may, for example, be near a border with another country or the proposal may involve the release of, say, a genetically engineered fish into a river that crosses international boundaries. Alternatively, the release may be capable of spreading, perhaps through the activities of birds, moths or other creatures, far beyond the release site itself. It is therefore right that countries that may be affected in this way should be consulted, regardless of whether or not they are members of the European Community, and that any comments they may have should be taken fully into account by the country authorising the release. We recommend that the UK authorities should, in appropriate circumstances, notify the competent authorities not only in other EC member states but also in other countries and should take full account of their views.

9.23 The notification arrangement has the other valuable function of enabling authorities in each member state to learn about activities elsewhere as an aid to developing their own understanding and experience. This is a useful proposal which will help to speed up the learning process that is necessary for assessing this new technology and should also help to foster uniform standards of assessment.

9.24 We have, however, two concerns about the draft Directive's proposals for 'the placing on the market of products containing or consisting of GMOs'. First, it is proposed that, reflecting the Community's 'single market' policy, once a product has been approved for release in one member state it should not be restricted in any other. Other member states would have the opportunity to object to a proposed release before the state in question endorsed it. If states were unable to agree, the CEC would itself decide the issue. We consider that this could lead to problems even with the introduction of non-living materials, such as chemical pesticides, into the environment and we note that there is currently no provision for Community-wide approval of pesticides. In our view, even more acute problems are raised by the

introduction of living organisms whose reproduction, spread and effect are very closely linked to the environment in which they exist. The assessment of a proposal to release a product which is or which contains a GEO must be related to the environment into which the release will take place. It cannot be assumed that a release which is acceptable in one locality will be equally acceptable under other environmental conditions. This potentially poses considerable problems even when the assessment is restricted to one country. It could, however, introduce major areas of concern once the decision becomes binding across a continent.

9.25 The draft Directive leaves open the opportunity to give geographically restricted approvals to product releases, no doubt because of the concerns described above. This might imply, however, a need for the national competent authority to which an application was made to consider whether the product should or should not be approved for release in various environments, including many with which it would not be familiar. Alternatively, each national competent authority would need to carry out its own assessment of every proposal, no matter in which country the application was made, against the possibility that the product might subsequently be released in its own country — an assessment which might have to be made with data which was inadequate for its particular circumstances. Neither of these would be satisfactory. We consider that the relationship between living organisms and their environment is such that proposed releases of GEOs must be considered in the appropriate environmental context. This aspect of the draft Directive needs further thought and should be the subject of careful discussion between the European Commission and member states.

9.26 Our second concern is that the proposals in respect of products are subject to a very extensive list of exclusions so that a high proportion of the frontrunners for early exploitation of the technology are excluded. Some of these exclusions, for example of pharmaceuticals, may be justified on the grounds that the product sectors are covered by other Community legislation; but in other cases, such as agricultural plants and animals, this is not so. In our view, the list of exclusions considerably weakens the value of the proposals. Where product controls exist, those responsible for them must, before they authorise release of a product which is or which contains a GEO, receive expert advice on those features which differentiate it from, for example, a chemical product. For products which are subject to no control, it is essential for the reasons given in paragraph 6.5 that controls should be established in respect of those which are or which contain GEOs. Member states will be free to adopt their own national controls over products which are excluded from the scope of the draft Directive, enabling each country to introduce whatever scheme it considers most appropriate to its circumstances. We nevertheless consider this to be less than satisfactory. Once released, organisms may become established and spread without recognition of national boundaries. It is therefore in everybody's interest to ensure that satisfactory and consistent regulatory procedures are installed as widely as possible.

9.27 The draft Directive on releases also specifies the information that should be required in order to assess whether a release should take place and how much of that should be made available to the public. Its proposals on this, including the provisions for commercially sensitive information to remain confidential, are very similar to our own set out in Chapters 6 and 8.

9.28 Although not of such direct relevance to this Report, we have also looked at the draft Directive for regulation of contained work on genetically engineered micro-organisms. This contains sections on waste disposal, on precautions against accidental release and on emergency plans in the event of

accidents. The proposals made have much in common with our own views set out in paragraphs 10.1–10.10.

9.29 During our discussions with officials of the CEC we also heard about their proposals for regular meetings of officials from member states to discuss and exchange information on release proposals, for an expanded research programme on biotechnology, in particular on risk assessment of releases (paragraph 10.25), and for the creation of a database of releases. These are all initiatives which should prove immensely valuable. We understand that similar activities by the European Community in relation to new chemicals have proved productive and we support these particular proposals by the CEC in the field of genetic engineering.

Developing countries

9.30 Biotechnology has generated much interest in the developing world with large genetic engineering programmes in many countries. International initiatives are being mounted through organisations such as the United Nations Industrial Development Organisation (UNIDO) and the United Nations Environment Programme (UNEP). UNIDO is helping to establish an International Centre for Genetic Engineering and Biotechnology which will carry out research to benefit developing countries and will have a major role in training scientists and technologists from such countries. UNEP supports Microbiological Resource Centres in Brazil, Egypt, Guatemala, Kenya, Senegal and Thailand. One UNEP programme of research focuses on environmental safety issues related to biowaste disposal and safety of release of GEOs. UNEP has also established, jointly with the World Health Organisation and UNIDO, an informal working group on the development of a process to assess potential risks and establish guidelines relating to biotechnology research, industrial processes and the environment([125]). This is a valuable step towards the adoption of internationally consistent practices and controls.

9.31 There are nevertheless fears in developing countries that the application of genetic engineering techniques there and in industrialised countries may affect them adversely. They are concerned that it may harm their economies through the increased scope for import substitution by the industrialised countries, hasten the loss of their diversity of genetic material through the use of new crop varieties, or encourage international companies to obtain property rights over the most productive varieties thereby denying developing countries free access to them. None of these concerns arises solely from the application of genetic engineering techniques but all may be exacerbated by it.

9.32 Our concern has focused on the prospect that restrictive regulation in some countries, notably those in the industrialised West, will encourage companies and research institutes to take advantage of less strict frameworks of control elsewhere. If any country allows releases to be carried out without thorough scrutiny, control and monitoring there will be a consequent risk to the environment and to health in that country and more widely. Recent publicity given to trials of rabies vaccine in Argentina, allegedly without the approval of the national authorities([126]), has highlighted this problem. This lends greater importance and urgency to the work being done in the OECD and under the auspices of the UN, referred to earlier in this chapter.

9.33 Notwithstanding the undoubted difficulties that biotechnology advances may bring in some cases, the field is nevertheless one that in general gives cause for optimism for developing countries. Successful applications are

likely to be concentrated in agriculture and health care. The relative ease of accessibility of the technology should help to ensure that the benefits to developing countries outweigh the disadvantages, though international action may be needed to direct research and development resources towards the crops and diseases of particular importance to them. Continued international action will be needed to encourage a consistent framework of control and to ensure that all nations are helped to develop their own abilities in this field in a co-ordinated fashion.

CHAPTER 10

OTHER MATTERS

Accidental release of GEOs

10.1 Concerns in the 1970s about possible hazards associated with genetic engineering led to the development of arrangements for containment of laboratory work in ways that would reduce the risks of harm to an acceptable level. In this country the Health and Safety Executive (HSE), on the advice of the ACGM and its predecessor the GMAG, issued guidance enabling laboratory experiments to be assigned to one of 4 levels of containment([67,111]). The procedure is discussed further in the box below. Other countries have procedures to achieve similar objectives. The OECD has published internationally agreed guidance on the subject which embodies the concept of 'Good Microbiological Practice'([78]).

GUIDELINES ON CONTAINED WORK INVOLVING GEOs

1. The HSE, on the advice of the ACGM and its predecessor the GMAG, has published guidelines on categories of containment for work involving GEOs. The categorisation scheme is designed to enable researchers and local safety committees to assign the appropriate degree of containment to an experiment involving GEOs. The scheme acknowledges that there is a risk of escape from all forms of containment and matches the tightness of the containment arrangements to the harm that an accidental release might cause. The procedure is based on an assessment of the harm the GEO could cause to people rather than to the environment.

2. The scheme sets down 4 categories of containment. Category I, the lowest level, is essentially a controlled laboratory used for work with GEOs run according to Good Microbiological Practice but with some additional facilities, for example to isolate work that generates a significant amount of aerosol. Category IV laboratories, at the highest level of containment, have very stringent requirements. They must be purpose built, have air-locks separating the laboratories from clean rooms, be provided with showers and be able to be completely fumigated. All material and effluent must be sterilised before it is destroyed or removed from the laboratory.

3. Three parameters are used to assess the risk posed by the GEO and hence the appropriate containment category. They are access to laboratory staff, expression of the cloned genetic material and damage. Access takes account of the mobility of many commonly used genetic engineering vectors and organisms and of their ability to enter the human body and survive in the gut. This is considered to be the most significant route of exposure for laboratory workers. Expression is a measure of the probability that the foreign genetic material in the manipulated organism will create products which will then be secreted from the GEO. Damage is a measure of the probability that these products will cause physiological damage in the body of the individual to which they gain access. Values are assigned to each of the parameters using guidelines provided by the ACGM.

10.2 The HSE, on the advice of its Advisory Committee on Dangerous Pathogens (ACDP), also issues guidance on the containment of pathogens. This applies to GEOs which are pathogens as well as to naturally occurring pathogens. There is close liaison, including cross-membership, between the ACGM and ACDP.

10.3 There have been very few known cases of failure in the laboratory containment of GEOs. One case where a laboratory worker was infected by an organism is discussed in the box below. The work involved laboratory research for medical purposes using disease-causing micro-organisms and would have come under the appropriate arrangements for work with pathogens. The case involved health risks for the laboratory staff rather than environmental damage. We have received no evidence that the contained use of genetic engineering techniques has led to any recognised harm to the environment.

AN ACCIDENT INVOLVING RECOMBINANT ORGANISMS

A laboratory worker was accidentally vaccinated with a recombinant vaccine containing material from the vesicular stomatitis virus. This virus causes a highly contagious brain disease in cattle, horses and pigs. In man it causes symptoms similar to influenza. The researcher developed no symptoms other than a swollen finger and lesions which took about 25 days to disappear. Analysis of serum from the researcher showed that he had developed antibodies to the virus. It is believed that the infection was mild either because the researcher had been vaccinated against smallpox about 30 years earlier or because the vaccine was attenuated([139]).

10.4 The absence of reported cases has helped to develop confidence in the technology as well as in the containment arrangements. Guidelines have been relaxed selectively as knowledge and techniques have improved. The guidelines for containment are based, however, entirely on the risk that the GEOs pose to humans. Potential harm to the environment from their escape is not taken into account. GEOs which are classified as plant or animal pathogens will be subject to controls under legislation concerned specifically with such organisms (paragraphs 7.14 and 7.15) but other GEOs may also pose risks to the environment as illustrated in Chapter 4. These latter organisms may often pose negligible risk to humans and so be assigned to the lowest level of laboratory containment. This may not, however, be adequate to protect against the environmental risks. We recommend that the ACGM, in consultation with the Release Committee, HSE, DOE and MAFF, should revise its containment guidelines to take this into account.

10.5 Accidental release could also occur from contained production processes. At present such processes using genetically engineered organisms are mainly devoted to the manufacture of medical products such as vaccines or diagnostic kits. Many industries have well-developed procedures for preventing and dealing with accidents. As the scale of genetic engineering activity increases it will be important for those involved with the production, storage, transport, use and disposal of the new products to take into account the lessons from accidents that have occurred in other industries. Our concern is with the prevention of harm to the environment but risks to human health and safety will also exist. The HSE has extensive experience and knowledge of the issues involved and must ensure that the industries concerned take the appropriate steps to reduce the risks, to the benefit both of people and of the environment.

10.6 In due course, however, a much wider range of products may be manufactured. The issues arising here are similar to those raised by chemical factories. Accidents in the use or storage of commercially produced GEOs may give rise to uncontrolled and possibly damaging releases. Risks of such accidents need to be considered when proposals for products which are or

which contain GEOs are put forward for assessment. Clear labelling, including instructions for storage, use, disposal and action to be taken in the event of an accident, should be considered where potential hazards exist. There are specific requirements for some of these in existing legislation and a general duty under section 6 of the Health and Safety at Work Act. We recommend in paragraph 8.18 that a power should be taken which would ensure that certain commercial products were used only by people competent to handle them.

10.7 Prevention is better than cure, so well-designed protocols for procedures at the laboratory, field trial site and production process plant are very important in reducing the risk of accidents occurring. Staff should be appropriately trained so that they understand how to handle the GEOs and associated equipment safely. Response plans should be drawn up to deal with the consequences of an accident and staff should be trained to implement them. We agree with the proposal of the European Commission([6]) that response plans should cover:

'— methods and procedures for controlling the GMOs in case of unexpected spread;

— methods of decontamination of the areas affected, for example eradication of the GMO;

— methods of disposal or sanitation of plants, animals, soils etc, that were exposed during or after the spread;

— methods for the isolation of the areas affected by the spread;

— plans for protecting humans and environmental health in case of the occurrence of an undesirable effect.'

10.8 Regulations already exist in the UK for the control of industrial hazards which could give rise to a major accident([127]). They include requirements to audit specific industrial sites (identified by the degree of potential hazard they pose) and to ensure that the site is as safe as is reasonably practicable with regard both to human health and safety and to minimising environmental damage particularly in the event of an accident, and to have emergency plans available including action to be taken on-site and by the local community in the event of an accident. Where the use or storage of GEOs in industry raises similar issues, similar precautions should be taken.

Waste arising from the production and use of GEOs

10.9 Sources of waste from the production and use of GEOs include laboratories, industrial sites and farms and may in future also include health care centres, schools and homes. Initial disposal routes may include landfill sites, sewage treatment works, incinerators, compost heaps and discharge to surface water. In many cases existing methods of disposal of biological waste, including procedures for handling pathogens, will be applicable to the disposal of GEOs. These include such procedures as the segregation of waste at source followed by sterilisation by pressurised steam or irradiation before disposal, landfilling including co-disposal, and incineration. The technique or combination of techniques appropriate in any particular case would depend on the nature of the GEO, the type of protein it is engineered to produce and its potential to cause damage to the environment. Her Majesty's Inspectorate of Pollution has experience of a wide range of waste disposal problems. We recommend that it should consider the issues in this area raised by the development of genetic engineering techniques and, in consultation with the appropriate authorities, issue advice on the selection of best practicable environmental options (BPEOs) for the disposal of the wastes.

10.10 When a proposed product which is or which contains a GEO is submitted for assessment (paragraph 8.9), a licence should be granted only if any waste or residue can be disposed of safely and if appropriate advice on waste disposal appears on the product label. There is already guidance for the disposal of biological wastes from hospitals([128]) and the discharge of biotechnological wastes from contained industrial processes to water is controlled. As the range of processes involving GEOs widens, guidance for the disposal of GEOs in biological and biotechnological waste, and its enforcement, should be kept under review to ensure that it remains appropriate. For example, as the use of GEOs in agriculture increases, farms will produce substantial quantities of waste originating from genetically engineered material. Methods of waste disposal must ensure, for example, that GEOs used as animal vaccines, or to protect crops or animals from pests or diseases, do not enter the food chain as animal or human food. At the same time consideration should be given to any potential hazards which might arise from the use of practices approved for certain chemical pesticides, such as disposing of surplus quantities by spraying it onto a dedicated area of uncropped ground. The waste disposal procedures recommended for field trials should also be kept under review.

Intellectual property rights

10.11 In Chapter 8 we recommend a degree of public access to information about releases which goes beyond the access allowed in respect of most products. Some of this information could be of commercial value to other companies. Indeed, the most basic information concerning the nature of the organism being released could be of great interest to a competitor as an indicator of a line worth pursuing. It is therefore important, as an adjunct to a regime of public access to information, that the information be covered by effective arrangements for statutory monopoly, that is by intellectual property rights.

10.12 The Patents Act 1977 provides that 'A patent shall not be granted for any variety of animal or plant or any essentially biological process for the production of animals or plants, not being a microbiological process or the product of such a process' (Section 1(3)). It has been possible to obtain protection for animals or plants produced by processes involving technical intervention, for example treatment of animals with antibiotics to increase weight gain. With this exception, however, animal and plant varieties obtained by traditional breeding techniques have been outside patent protection. Genetic engineering often involves microbiological processes. Patents have been granted in this country and overseas on genetically engineered micro-organisms and on the processes by which they were produced. Transgenic plants and animals may be considered to fall within the scope of the Act if they were produced by a microbiological process of genetic engineering, although this interpretation has yet to be tested in this country.

10.13 The UK patents system is constructed in such a way that its main provisions have, as nearly as practicable, the same effects as the corresponding provisions of the European Patent Convention. The Convention was recently interpreted by the European Patent Office (EPO) as not restricting the patentability of genetically engineered plants, as distinct from plant varieties. A recent application for a patent on a genetically engineered mouse has been provisionally rejected by the EPO but an appeal is likely to follow([129]). The Office is considering applications for patents on other animals. The UK Patent Office will take guidance from the EPO's decision.

10.14 Plant varieties have been granted protection under the Plant Varieties and Seeds Act 1964. This Act established procedures by which plant breeders

may claim rights over plant varieties, following the provisions of the Convention of the International Union for the Protection of New Varieties of Plants (the UPOV Convention). Briefly, the breeder may obtain a limited monopoly right over the varieties he produces, with payment of royalties by those who buy the plants or seed. The breeder may not, however, prevent a grower from retaining part of the crop for reuse as seed in later seasons. Nor do the breeder's rights extend either to the marketing of reproductive material intended for consumption or to the use of the variety in order to develop new varieties for whatever purpose. It is a condition of the UPOV Convention that no variety which is protected under its terms may also be subject to patent protection. There is no comparable framework for animal breeding.

10.15 In the USA provision is made in law for the patenting of plants as well as the protection of plant varieties. Patents have been granted on genetically engineered animals, including the mouse referred to in paragraph 10.13. Applications for patents on other animals are pending([130]).

10.16 We have received evidence([81]) to the effect that plant breeders' rights offer inadequate protection for their commercial interests now that genetic engineering techniques are available. (Animal breeders lack even this limited protection.) Opinions differ on this matter, but both the Ministry of Agriculture, Fisheries and Foods which administers plant breeders' rights, and the Patent Office, acknowledge the need to consider change([131,132]).

10.17 Intellectual property rights over living organisms raise many difficult moral and other issues. These include patent protection for transgenic animals, rights of farmers and breeders and the question of patents over variations of plant species native to developing countries (paragraph 9.31) which is a matter of current international debate. These issues are beyond the scope of this Report.

10.18 We received evidence([81]) about the disclosure of information on trial releases. For a chemical product there is normally a lengthy period of trials before an application is made for product approval. A patent application would be filed before the product approval application but after many of the trials had been carried out. In the case of a genetically engineered organism, because information would be publicly available at the stage of trial release, the patent application would probably have to be filed at an earlier stage in order to obtain the necessary protection.

10.19 The UK Patent Office is involved in discussions with other national Offices and interested parties, under the auspices of the World Intellectual Property Organisation, in an attempt to harmonise the law as it relates to biotechnology inventions. The European Commission is also developing proposals in this area. We do not wish to comment on these proposals, but we commend the flexibility of approach which the Patent Office and the European Commission are showing in this matter. It is important that a regime of intellectual property rights should be developed which provides sufficient protection to enable the release of adequate information to the public without undermining the commercial viability of the development and thereby damaging the incentive for innovation.

Public education

10.20 Our impression is that public awareness of the implications of the release of genetically engineered organisms to the environment is low. It is important that members of the public should receive sufficient readily

intelligible material to allow a considered individual view to be formed. We hope that our own Report will stimulate a debate not only of the benefits offered by the development and use of GEOs, and the risks entailed by their release to the environment, but also of the present and proposed mechanisms for assessing the risks and for deciding whether a release should go ahead.

10.21 Knowledge of genetics and ecology should be included in the curriculum in schools. We were encouraged to see some of the teaching material on the techniques of biotechnology which has been produced for GCSE([133]) and A Level([134]) students but it is important that students should also be aware of the factors involved in judging the impact on the environment of a proposed release.

Research

10.22 A continuing theme of the discussion in preceding chapters of this Report about the risks to the environment from the release of GEOs has been the gaps in knowledge and understanding of the behaviour of organisms in the environment. Filling these gaps is an important area of research in the UK and overseas.

Current programmes

10.23 The US National Science Foundation Workshop on microbial ecology in 1986 identified research in the following areas as important to support the release of GEOs([135]):

- fitness of GEOs for survival;
- genetic material transfer;
- long-term food-chain and population data;
- improved detection methods;
- effects and prediction of dormancy and shut down states;
- gross metabolic effects as measured by the nitrogen or carbon cycles;
- techniques for monitoring population levels;
- microbial taxonomy;
- effects of selective pressures at community level;
- predictive uses of microcosms.

10.24 In 1986 the US Environmental Protection Agency spent $4.4 million on biotechnology risk assessment and in 1987 had allocated $5.7 million. A proportion on each occasion was dedicated to assessing the risks of releasing GEOs. Early work included such environmental issues as the risk of spreading genetically engineered micro-organisms from sewage treatment works and in aerosols. Their current research on the environmental fate and effects of GEOs released to the environment includes([8]):

- genetic transfer, stability, and ecosystem effects;
- factors influencing gene expression in the environment;
- the role of position effects on genetic stability, for example transposons, chromosomes and plasmids;
- reliable detection, identification and enumeration of genetically engineered micro-organisms;

- methods and protocols for laboratory studies;
- preparation of risk assessment guidelines;
- evaluation and modification of methodologies in microcosms;
- extrapolation of microcosm to field data;
- use of microcosms to detect gene transfer.

10.25 The European Commission is keen to initiate collaborative research amongst member states into biotechnology risk assessment. An example of this was the project undertaken by institutes in France, Germany and the AFRC Rothamsted Experimental Station in the UK on the movement of genetic material in the soil using an antibiotic resistant marker in *Rhizobium* (Appendix 5 paragraph 21), which was sponsored by the EC's Biotechnology Action Programme (BAP). BAP is being reviewed and the programme which replaces it, Biotechnology Research for Innovation, Development and Growth in Europe (BRIDGE), will not only contain larger projects but will also devote more resources to research into risk assessment([86]).

10.26 In the UK the Department of Trade and Industry has launched a joint programme with the AFRC and industry to provide information which will help in the development of protocols for the testing and assessment of GEOs. This initiative, known as PROSAMO (planned release of selected and manipulated organisms), is a 3 year programme starting in 1989. It is anticipated that it will cost £1.5 million in total and will concentrate on two main areas([136]):

- the possible spread of released bacteria and genetic material in soil (centred on the Universities of Aberdeen and Essex);
- the possible spread of released genetic material via pollen and insects within and between selected crops (centred on Imperial College, Silwood Park and the AFRC Institute of Plant Science Research at Norwich).

In the course of the programme it is hoped that more will be learnt about:

- monitoring techniques for low populations of bacteria in soil;
- the degree and methods of gene transfer between soil bacteria and between plants;
- the ability of selected genetically engineered crops to survive in the environment.

10.27 The Department of the Environment has embarked on a research programme aimed at improving aspects of risk assessment for releases. The aims and funding of the programme are summarised in the box on page 80([137]). The Research Councils, particularly NERC and AFRC, also have research projects relevant to risk assessment for the release of GEOs([20,138]).

Prospective research

10.28 It is the Commission's firm view that there is a need for a substantially enhanced research base in the basic sciences underpinning the release of genetically engineered organisms to the environment. The reason for seeking to secure this enhanced research base is that the science is developing and changing so quickly, and the opportunities for exploitation are so great in the longer term, that without this continuing research base we may be unable to address the new and unexpected issues which will surely arise.

10.29 We believe that this increased research base should be located in the universities and research institutes and should receive adequate funding. Such research should be in three major areas: the molecular biology of organisms in the environment, interactions between organisms and the environment and basic studies on ecology and population biology.

10.30 This basic research should be supplemented by projects related to specific environmental issues commissioned by the relevant Government departments.

DOE RESEARCH PROGRAMME ON THE DELIBERATE RELEASE OF GENETICALLY ENGINEERED ORGANISMS

1. The current research priorities of the DOE are:
   - techniques for the extraction, identification and quantification of micro-organisms, in particular soil micro-organisms;
   - studies on factors governing the persistence and spread of organisms, in particular micro-organisms;
   - studies on the possible loss of constructs from engineered to native organisms, including a consideration of the role of free DNA and viruses;
   - technology for the containment of field trials and emergency clean-up.

2. Expenditure on the research programme was nearly £130,000 in 1987/88, rising to £290,000 in 1988/89. Estimated expenditure in 1989/90 is about £650,000. Further growth is expected in 1990/91. Current studies include the ecology of micro-organisms on and in birds and other small animals, improved techniques for the identification and extraction of soil micro-organisms, the role of transposons in mercury resistance and a survey of past UK introductions of exotic animals.

3. The DOE is a member of the Interdepartmental Committee on Biotechnology, the secretariat of which is provided by DTI's Laboratory of the Government Chemist. This committee provides a forum for the Government departments and the Research Councils to liaise on and to co-ordinate the development of their research programmes in genetic engineering. In addition the DOE has close working arrangements with those concerned with the NERC research programme in this field and is developing its links with AFRC. DOE were also involved in the design of the joint industry/Government PROSAMO initiative (paragraph 10.26).

10.31 In the course of this study a number of areas have been mentioned to us as requiring further research. On the genetic engineering side these include the following:

- The development of good genetic markers to detect and trace the movement of GEOs and any added foreign DNA in the environment. Quick and easy monitoring methods are also required, particularly when small animals, plants or micro-organisms have been released.
- To reduce the likelihood of a GEO being persistent, it may be debilitated in some way or equipped with a self-destruct mechanism such as a suicide gene. This is discussed in Chapter 6. Because of the potential importance of these mechanisms research is needed to ensure that they work in the environment when they are required and that they cannot easily be lost from the GEO.

- Research on the functioning of a GEO which has had a foreign gene added to it is needed. This could increase the understanding and control of expression of the added gene or genes or show whether the addition of the new gene has altered the GEO in any other way.

10.32 Basic ecological research is of particular importance to an understanding of the release of GEOs and has to be adequately funded on a continuing basis. Some of the areas which were mentioned during the study are as follows:

- Basic microbial ecology and taxonomy, to increase the ability to isolate, characterise and identify micro-organisms in natural, semi-natural and agricultural landscapes and to understand their population dynamics, modes of dispersal, resting stages and species interactions.
- Fundamental work on the genetics and evolution of micro-organisms in the environment. Work of this kind would broaden understanding of the ways in which GEOs might behave under field conditions and hence reduce the risk of unexpected responses.
- The influence of environmental factors on gene movement and survival, for example via pollen transfer in flowering plants or via plasmids and other mobile genetic elements in micro-organisms. Considerable scope exists for both theoretical and empirical work in this area.
- Work aimed at developing a better understanding of the interactions between natural communities of plants, animals and micro-organisms and how the properties of the component populations determine the stability and resilience of whole communities.
- Methods for monitoring the environment in the area of a release to detect environmental problems that might not have been anticipated when planning the release. It is impossible to monitor all species at a release site. Work therefore needs to be done on the selection and study of suitable indicator species or small groups of species at various points in the food web. Much may be learnt from studies of past releases (deliberate or accidental) of non-genetically engineered organisms into alien environments to try to discover whether any general kinds of monitoring programmes might have helped to recognise problems at an early stage.
- Research on the way information obtained in laboratory and microcosm experiments may be related to the behaviour of organisms in field trials and the environment. It would also be useful to know which of the information obtained during field trials is of use in predicting the effects of a genetically engineered organism on the environment when it is used as or in a commercial product and hence on a much larger scale. Work under this heading covers a wide range, from the need to develop suitable laboratory microcosms to theoretical studies on population invasion and establishment over different spatial and temporal scales.

CHAPTER 11

SUMMARY

Scope of the Report

11.1 The biological behaviour of living organisms, from the most complicated animals and plants to the simplest microbes, is determined by their genes. Genetic engineering is concerned with deliberately changing the genes of an organism in order to alter one or more of its characteristics. This Report is about the environmental issues raised by the release of such genetically engineered organisms (GEOs). It discusses the effects that releases might have on the environment, the procedures necessary to identify, assess and minimise any risks to the environment and the regulatory arrangements needed to ensure protection for the environment.

11.2 Genetic engineering raises issues across a wide spectrum—ethical, social and political as well as environmental. Issues such as animal welfare, the possible loss of genetic diversity through the promotion of fewer crop varieties and the possibilities of military or terrorist use are touched upon very briefly in this Report. Other important issues, however, such as human gene therapy, human embryo research and the fundamental question of whether mankind should seek to create new forms of life, fall outside our remit and are not considered.

Natural genetic change

11.3 Genetic change occurs continuously in nature. This may be the result of mutations or of new combinations of genes created by fertilisation of eggs, pollen transfer or other DNA exchanges. The differences between individuals that arise from these processes allow natural selection to occur.

11.4 For centuries man has made use of the natural processes of genetic change to breed new strains of plants and animals. Increasing sophistication of techniques has enabled plant and animal breeders to make major advances in disease resistance, yield, quality and many other economically desirable attributes of crops and in the appearance, physiology and other characteristics of animals. Relying on the artificial selection of individual plants or animals and intensive propagation methods, breeding techniques generally allow new strains to be developed in a minute fraction of the timescale of natural evolution. The resulting new varieties differ only in degree, however, from the strains from which they were developed.

11.5 In general the selection and refinement of particular traits in this way is not considered an environmentally damaging activity. It has, however, indisputably changed our environment with the appearance of the countryside reflecting farming practices based on modern breeds and plant varieties. In addition, some crop varieties are dependent on artificial support, such as irrigation, fertilisers and pesticides to produce optimal yields. These too have an impact on the environment.

Genetic engineering

11.6 Over the past 40 years, developments in understanding of genetic structure and its manipulation have opened up new possibilities for engineering genetic changes. Several laboratory techniques now exist by which a specific gene can be removed from an organism and inserted into a different

organism where it replicates and functions. Such 'genetically engineered' organisms may contain genetic information and exhibit properties that have evolved in the context of an unrelated species. The organisms may contain combinations of genes that are extremely unlikely to have occurred in nature in situations in which the organisms in question could multiply. Genetic engineering allows genes from almost any organism to be introduced into almost any other organism, regardless of sexual compatibility or evolutionary relationship. In this respect it is qualitatively different from traditional breeding techniques.

11.7 Progress in breeding techniques has, however, produced a grey area of overlap between them and genetic engineering. For this reason, and also because of rapid development in the science of genetic engineering itself, it is not easy to arrive at a precise definition of genetic engineering. The essential feature is the deliberate 'engineering' of an organism's nucleic acid. This may involve the insertion of genes from other organisms, the rearrangement or duplication of genes, the deletion of genes or the construction of novel genes. Techniques which come within this concept of genetic engineering include recombinant DNA (rDNA) techniques, micro-injection and protoplast fusion. In our view, whether a process is considered to be genetic engineering depends on the technique involved and not on whether the outcome might have occurred naturally and an organism should not be excluded from consideration simply on those grounds. This is of particular relevance in the case of gene deletions. It is important that any definition should be kept under review.

11.8 We adopt the Health and Safety Commission's definition of a deliberate release to the environment, namely any use 'without provision for containment such as special procedures, equipment and installations or facilities that provide physical barriers to minimise [the organism's] spread (and that of its nucleic acid) to the environment.'

Biotechnology

11.9 Genetic engineering at present represents a small proportion of all the activities classed as biotechnology, which also encompasses processes as traditional as cheese making and brewing. Many processes involving biotechnology take place in contained facilities such as vinegar factories. There is also, however, a long history of organisms used by man in the open environment as well as the traditionally bred crop plants and animals discussed above. Many pesticide preparations based on naturally occurring viruses are commercially available. The soil bacterium *Rhizobium* is used worldwide to improve the growth of peas, beans and related crops. The technology of genetic engineering will make possible an enormous increase in the number of releases, in the diversity of the organisms released and in the scale on which the releases take place.

11.10 Vaccines, drugs and diagnostic kits developed using genetic engineering techniques are already on the market. New pest resistant plants are being developed. Applications in food processing, pollution control and many other areas are likely to follow.

The environmental impact of released organisms

11.11 As with many new technologies the potential for improvement is accompanied by a risk of undesirable effects. Releases have so far been on an experimental scale and have had no known adverse environmental effects. Organisms which survive and become established could, however, affect the environment in a variety of ways—both beneficial and undesirable. Some

releases may alter the diversity of species in the environment. Such effects could produce noticeable changes in the countryside and could have an economic impact. Some organisms could pose a threat to human health. At the most extreme, new organisms could conceivably affect major environmental processes such as weather patterns, the nitrogen cycle or other regenerative soil processes.

11.12 One of the first releases of a GEO in Great Britain was of a genetically engineered virus. The unmodified virus attacks only specific caterpillars and has been used safely as a biological insecticide for years but, in comparison with chemical pesticides, it is slow acting. The release was carefully assessed to ensure it posed no unacceptable risks. Manipulation of a virus for a particular purpose could, for example, alter other characteristics such as virulence or the range of susceptible organisms in a harmful and unintended way.

11.13 Where plants are being engineered to kill insects that feed on them, the possibility that people and other non-target animals might be affected must be borne in mind. Also, cultivation of the engineered plant over a large area may encourage the development and spread of insects resistant to the toxin, particularly if the relevant gene were to spread to other plants, for example by pollen transfer. Spread of the gene might also result in other, non-target insects falling victim to the toxin.

11.14 Paragraphs 4.8–4.11 and Appendix 5 summarise other releases, all field trials, and the environmental concerns that have been raised about them. In view of the limited experience of the release of GEOs to the environment, it is helpful to study the effects of releasing non-engineered organisms to the environment, although they do not necessarily provide an exact analogy for releases of GEOs.

11.15 There are many well-researched cases of the environmental impact of exotic species introduced into new environments. Some examples are given in Chapter 4. It is estimated that about 1 in 10 of the known introductions of alien species of plants, animals and micro-organisms into the British Isles have become established. Of these about 1 in 10 have in turn become pests, varying in severity from relatively minor to highly damaging.

11.16 Some GEOs may be expected to have similar impacts on the environment to those produced by new varieties of traditionally bred crops and ornamental plants. If a new crop variety is commercially successful it will be grown on large acreages and may have a significant environmental impact. In addition, although many domesticated animals and crop plants cannot survive for long without man's intervention, some domesticated animals have established self-sustaining, feral, populations in the wild. Similarly, some crop plants, for example oilseed rape, have become established on non-agricultural land. Often ferals, like weeds, have become pests.

Assessing the risks

11.17 Although the environment is generally resilient, resistant to invasion by alien organisms and robust to biological perturbations, it is probable that some organisms, once released to the environment, will become established there. Most are likely to pose no hazard but others may cause varying degrees of disturbance which, in the extreme, could have serious environmental consequences.

11.18 The prediction of environmental impacts is difficult. However, many proposed releases will concern domesticated animals or crops whose behaviour is much better understood than that of many wild species.

11.19 Industry is unlikely to be interested in deliberately introducing organisms which might spread uncontrollably or find a permanent niche in the environment. However, genetic engineering makes it possible to remove, deliberately or accidentally, the genetic limitations which prevent some crops from becoming nuisances. In addition, after release, GEOs will themselves be subject to natural selection pressures affecting their environmental fitness.

11.20 The extent to which genes, especially novel genes, may spread to other organisms is an important uncertainty in assessing the risks in the release of GEOs. It will be prudent to begin with the assumption that an introduced gene could spread widely and then to challenge that assumption.

11.21 The risk of inadvertently converting harmless organisms into environmentally deleterious ones appears to be low. Pathogenicity involves the combined effects of many genes. The same is true of a plant's ability to become a troublesome weed. Some organisms, however, already possess many of the necessary genes and may, indeed, be related to known pathogens or weeds. When such organisms are being manipulated, they need to be scrutinised to ensure that they have not been converted into a threat to man or the environment.

11.22 The release of viruses offers potential benefits. Because the genome of a virus can be so small, however, its manipulation may have a more significant and unexpected effect than the manipulation of a plant or animal. Viruses, particularly retroviruses, are also useful as vectors in genetic engineering, particularly of animals. The use of retroviruses poses risks, however, and the release of retroviruses or of organisms manipulated using them should be approached with the utmost caution.

11.23 Concerns in the 1970s about the safety of genetic engineering work in laboratories led to stringent containment arrangements which have gradually been relaxed as confidence has increased. As large gaps still exist in knowledge about behaviour of organisms in the environment, an initially cautious approach, taking account of the ingenuity that scientists will apply in the development of new organisms, is the responsible way forward.

11.24 It may be possible to recover or eradicate come plants or animals after release if this proved necessary. Birds, fish, small mammals or insects are, however, likely to be irretrievable once released. Eradication of plants should be possible by methods including appropriate herbicides but once a variety has been released commercially its progeny may be used by plant breeders on a wide scale for crossing with other plants. Eradication of an introduced gene from all offspring could then be extremely difficult.

11.25 The implications of this wide dissemination need to be taken into account when considering commercial releases of plants. Viable samples of current commercially-used varieties should be conserved so that these can be returned to if necessary in the future. There should be lineage registers recording the history of plant varieties including information on introduced genes. In addition, before organisms with introduced genes are released the introduced DNA sequence for the new genes should be characterised for future reference.

11.26 Some disease-causing micro-organisms have been successfully eradicated either globally, for example smallpox, or locally, for example outbreaks

of foot-and-mouth disease. In general, however, eradication is difficult, costly and not always successful. The extent to which a GEO, or genes that might spread from a GEO to other organisms, can be recovered or eradicated from the environment will be an important factor to consider before a release takes place.

11.27 DNA is a chemical and large amounts are added to the environment as a result of the natural processes of excretion, death and decay of organisms. This DNA, like most other common biological material, is generally rapidly degraded. In some environmental conditions it can become more resistant to degradation but very little is known about the frequency of this or its consequences. As genetic technologies develop, specially constructed nucleic acid molecules might be produced which would require careful disposal. Some might resist biodegradation.

11.28 It seems likely that, in many situations, biological products could be safer and less polluting than non-biological alternatives. However, a selective, readily degradable chemical pesticide leaving no objectionable residues and which is non-toxic to humans, could it be designed, might have an advantage over biological products. Research in this direction should not be abandoned and nor should the development of agricultural practices such as integrated pest management which reduce the need for pesticides.

Procedures to minimise risk

11.29 Organisms which are pathogenic are already the subject of legislative control in this country. Many other organisms, including micro-organisms, are harmless or even beneficial. Many issues relating to behaviour of organisms in the environment are not readily susceptible to research in laboratories or contained artificial environments. Experiments in the field, carefully monitored and using GEOs that offered negligible risk, would make a greater contribution to safety than a moratorium on releases. If the recommendations in this report are implemented, it should be possible to identify proposals for release that raise concerns and deal with them appropriately on an individual basis, if necessary preventing them from proceeding. We see no environmental justification for preventing releases which are considered safe from proceeding. Our proposals would allow these to go ahead with any necessary safeguards.

11.30 Some GEOs, for example pesticides or food additives, will be subject to existing product controls. Where these controls exist they should be the primary channel for assessing relevant GEOs. However, GEOs need an extra degree of scrutiny by people with particular knowledge of their behaviour and the ability to judge their environmental impact. Such a scrutiny is also needed where no product controls exist. In due course, accumulating experience may lead to a reconsideration of controls directed specifically at GEOs in favour of reliance on wider product controls. It would not, however, be prudent to take this approach in the current state of knowledge.

11.31 At this stage of the development of the technology, every proposed release should receive a thorough scrutiny by a national committee of experts (the Release Committee). Prior to such scrutiny a local committee based within the organisation developing the GEO should screen the proposal to ensure that only well thought out proposals come forward for national scrutiny. In due course it may be possible to identify types of release which would require only local scrutiny. This should not be done until considerably more experience of releases has been obtained.

11.32 It has been widely suggested that categories of organism should be drawn up and that proposals for release should be treated differently according to the category in which they fell. This is a desirable and achievable objective but it would be imprudent at present to define categories which may be exempted from scrutiny. Case by case assessment of every proposal to release a GEO is essential. This need not result in undue burdens. Many proposals will raise similar issues. Scrutiny can concentrate on novel aspects of the environment or the organism. The information to be provided will be less in cases which are well understood and will depend on the uncertainties inherent in the proposal, modified as necessary in the light of information acquired as the release progresses.

11.33 The information provided to the Release Committee should provide convincing evidence that the proposer has carried out a thorough risk assessment and should be sufficiently detailed for the Committee to make an informed judgment of the risks associated with the proposed release. Research programmes in progress or planned should help to fill gaps in knowledge. We endorse the approach that the Advisory Committee on Genetic Manipulation is taking in its revision of the guidelines for information and risk assessment.

11.34 In addition, procedures are needed that will encourage people to think of possibilities that might not otherwise have been considered. A technique known as HAZOP is used for this purpose in the chemical industry. The Commission is developing this technique for the different context of release proposals.

11.35 Creating artificial environments, known as microcosms, where a GEO's behaviour can be examined before release, could be a useful way of reducing risks to the environment. It can be difficult, however, to relate the results from microcosm experiments to the behaviour of organisms in the environment. They are also difficult to use with large animals or plants.

11.36 Risks can be further reduced by ensuring that the uncertainties introduced at each stage of development of new organisms are limited. The progression from laboratory to widespread release should proceed through a series of stages gradually relaxing the degree of containment at each. In addition, there should be a step-by-step approach to innovation in the releases that take place so that the modifications made at each step do not introduce an unacceptable degree of uncertainty.

11.37 Methods of engineering debilitating mechanisms into organisms, particularly micro-organisms, are being investigated to minimise any risk of unwanted persistence in the environment. The systems may not be totally effective and in some circumstances it may not be practicable to use them. Debilitation may nevertheless often be useful to reduce risks associated with a release, particularly during experimental field trials. Physical restrictions on the spread of released organisms and arrangements for eradication with chemicals are also to be encouraged where practicable.

11.38 Releasers should be given clear advice about the manner in which releases should be carried out, including arrangements for security, monitoring, clean-up and contingencies. Compliance with these arrangements should be checked by inspectors. The extent, methods and arrangements for monitoring the outcome of a release should be considered by the Release Committee when assessing a proposal. This will need to cover the spread of the GEO and any introduced genes, the environmental impacts of the release and any unexpected ecological event. Stable marker sequences associated

with the added genetic material may be desirable to aid monitoring. The use of antibiotic resistance markers needs to be considered against a background of increasing concern about the spread of antibiotic resistance in the environment. It would be highly undesirable if the release of a GEO accelerated the dissemination of antibiotic resistance genes in pathogens.

11.39 General monitoring of the environment can also be useful in detecting or testing for unexpected changes. There is scope for co-ordination in this area, building on the work of voluntary organisations and others to develop a systematic approach. The DOE should take the lead in promoting and funding this.

11.40 The Release Committee should identify certain categories of information about the results of release experiments which it will expect to receive on completion of or possibly even during the experiments. The committee should carry out regular reviews of the information it has obtained about the outcome of releases. International exchanges of information between assessment bodies could also provide valuable material to assist in assessing release proposals. An international database of releases would be of immense value in the early years of release activity.

Regulation

11.41 Some existing legislative measures could, in principle, be used to control the release of GEOs to the environment. Each is limited in the range of organisms to which it applies and even taken together they do not provide complete coverage. The HSE operates a voluntary notification system, shortly to be given statutory backing under powers in the Health and Safety at Work Act 1974. This Act cannot, however, be used to control releases which present risk to the natural environment but which do not affect human health or safety. For this a separate and new power is required. The Secretary of State for the Environment* should take primary responsibility for control with respect to the environmental consequences of releases of GEOs.

11.42 New powers should complement the provisions of the Health and Safety at Work Act and should evolve from existing arrangements. A statutory duty of care should be imposed on those responsible for releases. The legislation should provide a framework enabling the Secretary of State to make regulations which can be amended to keep pace with technology, knowledge and experience.

11.43 A release licence should be required before a release may take place. Licences should be issued by the Secretary of State for the Environment and the HSC acting jointly on the advice of a Release Committee. Those responsible for releasing GEOs should also be required to be registered. Detailed recommendations for regulation, including provisions for monitoring and for public access to information, are listed in Chapter 12.

11.44 The imposition of strict controls on the release of genetically engineered organisms may increase incentives to select and develop non-engineered organisms. The result could be a threat to the environment as great at that posed by some GEOs. The Government should review the issues arising from this.

International aspects

11.45 Denmark and Canada have comprehensive legislation dealing with deliberate release of GEOs. Other countries are considering legislation or,

* Here and throughout this chapter, references to the Secretary of State for the Environment and to DOE should be taken as applying also to their territorial equivalents in Wales, Scotland and Northern Ireland.

like the USA, are using legislation enacted for other purposes. The OECD has set up working groups to look at various aspects of release. We strongly support these activities of the OECD and hope that the UK Government will continue to play a major and positive role. UNEP is also considering the subject.

11.46 The European Commission has published a draft Directive on release. The proposals for regulation of experimental releases have many similarities to our own. We have two concerns about the proposals for the marketing of products containing GEOs.

11.47 First, it is proposed that once a product has been approved for release in one member state it should not be restricted in any other. We consider that the relationship between living organisms and their environment is such that proposed releases of GEOs must be considered in the appropriate environmental context. This aspect of the draft Directive needs further thought and should be the subject of careful discussion between the European Commission and member states. Secondly, the extensive list of exclusions from the products section of the draft Directive considerably weakens the value of the proposals.

11.48 The draft Directive has proposals for public access to information which are very similar to our own. A separate draft Directive on contained work on GEOs has proposals on waste disposal, on precautions against accidental release and on emergency plans in the event of accidents, which have much in common with our own views on these topics.

11.49 We support proposals by the European Commission for regular meetings of officials from members states to discuss and exchange information on release proposals, for an expanded research programme on biotechnology, in particular on risk assessment of releases, and for the creation of a database of releases.

11.50 The field of biotechnology is one that in general gives cause for optimism for developing countries. There are, however, some fears in developing countries that the application of genetic engineering techniques may exacerbate problems such as the loss of markets for their products in industrialised countries. Our concern has focused on the prospect that restrictive regulation in industrialised countries will encourage companies and research institutes to take advantage of less strict frameworks of control elsewhere. This lends greater importance and urgency to the work being done in the OECD and under the auspices of the UN. Continued international action will be needed to encourage a consistent framework of control and to ensure that all nations are helped to develop their own abilities in this field in a co-ordinated fashion.

Other matters

11.51 The ACGM, in consultation with the Release Committee, HSE, DOE and MAFF, should revise its guidelines on contained work involving GEOs to take account of potential harm to the environment from the escape of GEOs.

11.52 The risks of accidents in the use or storage of commercially produced GEOs need to be considered when proposals for products which are or which contain GEOs are put forward for assessment. Clear labelling, including instructions for storage, use, disposal and action to be taken in the event of an accident, should be considered where potential hazards exist.

11.53 As the scale of genetic engineering activity increases it will be important for those involved with the production, storage, transport, use and disposal of the new products to take into account the lessons from accidents that have occurred in other industries. The HSE must ensure that the industries concerned take the appropriate steps to reduce the risks. Protocols aimed at reducing the risk of accidents occurring are very important. Staff should be appropriately trained. Response plans should be drawn up to deal with the consequences of an accident.

11.54 Her Majesty's Inspectorate of Pollution (HMIP) should consider the waste disposal issues raised by the development of genetic engineering techniques and, in consultation with the appropriate authorities, issue advice on the selection of best practicable environmental options (BPEOs) for disposal of the wastes. When a proposed product which is or which contains a GEO is submitted for assessment, a licence should be granted only if any waste or residue can be disposed of safely and if appropriate advice on waste disposal appears on the product label. As the range of processes involving GEOs widens, guidance for the disposal of GEOs in biological and biotechnological wastes, and its enforcement, should be kept under review to ensure that it remains appropriate. The waste disposal procedures recommended for field trials should also be kept under review.

11.55 In Chapter 8 we recommend a degree of public access to information about releases which goes beyond the access allowed in respect of most products. Some of this information could be of commercial value to other companies. A regime of intellectual property rights should be developed which provides sufficient protection to enable the release of adequate information to the public without undermining the commercial viability of the development and thereby damaging the incentive for innovation.

11.56 We hope that our Report will stimulate a debate on the benefits offered by the development and use of GEOs, the risks entailed by their release to the environment and the present and proposed mechanisms for assessing the risks and for deciding whether a release should go ahead. Knowledge of genetics and ecology should be included in the curriculum in schools. Students should be aware of the factors involved in judging the impact on the environment of a proposed release.

11.57 There is a need for a substantially enhanced research base, located in the universities and research institutes, in the basic sciences underpinning the release of GEOs to the environment. This basic research should be supplemented by projects related to specific environmental issues commissioned by the relevant Government departments.

11.58 Areas mentioned to us as requiring further research on the genetic engineering side include:

- the development of good genetic markers to detect and trace the movement of GEOs and any added foreign DNA in the environment, and of quick and easy monitoring methods, particularly for small organisms;
- validation of debilitation mechanisms in the environment;
- understanding and control of gene expression by engineered genomes.

11.59 Basic ecological research is important and has to be adequately funded on a continuing basis. Some areas mentioned during the study are:

- basic microbial ecology and taxonomy;
- the genetics and evolution of micro-organisms in the environment;
- the influence of environmental factors on gene movement and survival;
- interactions between natural communities of plants, animals and micro-organisms;
- methods for monitoring the environment in the area of a release;
- relation of laboratory and microcosm experiments to the behaviour of organisms in field trials, and relation of field trial results to the impact of a commercial product in widespread use.

CHAPTER 12

RECOMMENDATIONS

Recommendations for the regulation of release

12.1 Statutory control of releases of genetically engineered organisms (GEOs) to the environment must be put in place. (8.1)

12.2 Both the Secretary of State for the Environment and the Health and Safety Commission (HSC) (acting on behalf of the Secretary of State for Employment) should be involved in decisions on release. (8.4)

12.3 The Secretary of State for the Environment* should take primary responsibility for control with respect to the environmental consequences of such releases. (8.1)

12.4 The control of releases of genetically engineered organisms should be governed by a statute establishing controls in respect of environmental protection and providing a framework within which the Secretary of State would be empowered to make regulations including a system for licensing. The statute should, in addition, impose a duty of care obliging all those responsible for the release of a GEO, whether for experimental or commercial purposes, to take all reasonable steps for the protection not only of human health and safety but also of the environment. (8.5)

12.5 A licence, which we refer to as a release licence, should be required before the release of a genetically engineered organism may take place. It should be an offence, carrying a substantial penalty, to release a GEO without having first obtained a release licence or to fail to comply with any conditions attached to the licence. (8.6)

12.6 Any release licence should be granted by the Secretary of State for the Environment and the HSC (referred to as the licensing authorities) acting jointly. They should also have the power to revoke a release licence or to amend its terms if they had reason to believe that the continuation of the licence was inadvisable. (8.6)

12.7 Anyone proposing that a GEO be released into the environment should be required to notify the licensing authorities of his intention and to furnish them with details of the organism concerned and the method of release, including the results of an assessment of safety carried out by a local safety assessment committee. (8.6)

12.8 The new Genetic Manipulation Regulations should be revised to provide that the HSC's approval to release be given in the form of a licence. (8.7)

12.9 In the light of experience the licensing authorities may consider it to be safe to issue a release licence for a class or category of related GEOs. Persons or organisations wishing to make releases under such a licence should, however, be required to submit their proposals to the licensing authorities who would decide whether they fell within the scope of that licence. The

* Here and throughout this chapter, references to the Secretary of State for the Environment and to DOE should be taken as applying also to their territorial equivalents in Wales, Scotland and Northern Ireland.

authorities should have the power to require that any proposal with features which gave rise to concern should be the subject of an application for a specific release licence, even though it appeared to be covered by a licence for a category. (8.8)

12.10 Each stage of release in the development of a GEO should be the subject of a licence. The organism may then be proposed for use as or in a product. It should be assessed once more at that stage and be subject to licensing by the licensing authorities for sale, supply or use as or in a particular product. If no other product control applies to that product the licence should be issued directly by them. (8.9)

12.11 Where other product controls apply, the product control authority should be required to inform the licensing authorities of any application for approval of a product which is or which contains a genetically engineered organism. They in response would inform the product control authority whether they were willing to issue a licence for the product. This applies both to products developed in this country and to those imported. Anyone applying for approval to the sale or supply of a GEO as or in a product should therefore be required to state in the application that it is genetically engineered. (8.9)

12.12 The Secretary of State for the Environment should be given additional powers including the power to: set up advisory committees; draw up and publish codes of practice; maintain a register of people and organisations approved to carry out releases; make information available to the public and to other authorities; deal with emergencies and impose obligations on others to establish emergency arrangements; carry out or require others to carry out appropriate monitoring; require the provision of information about releases; require the proper disposal of waste products and, if necessary, cleaning up of release sites; inspect premises; and recover the costs of regulation. (8.10)

12.13 The Government should consider whether the powers of the HSC need to be extended, in respect of the release of GEOs, to cover some or all of the powers listed in recommendation 12.12 which it does not already exercise. (8.10)

12.14 The first consideration in the proper control of releases of GEOs is a thorough, expert scrutiny of every proposed release. At this stage of the development of the technology we consider that each case needs to be scrutinised by a national committee of experts. Prior to such scrutiny a local committee based within the organisation developing the GEO should screen the proposal to ensure that only well thought out proposals come forward for national scrutiny. (6.6)

12.15 The Secretary of State for the Environment and the HSC should refer each application for a release licence, or for product approval, in respect of a genetically engineered organism, to a committee of experts and should take account of its recommendations. The primary function of the committee should be the assessment of such proposals with regard to environmental protection and human health and safety. (8.11)

12.16 The present Intentional Introduction Sub-Committee of the Advisory Committee on Genetic Manipulation (ACGM) should be constituted as a committee in its own right, distinct from the ACGM. It should be charged with giving advice to both the HSC and the Secretary of State for the Environment. We refer to it as the Release Committee. (8.11)

12.17 The Release Committee should have close links with the ACGM. This may be achieved through common membership and a joint secretariat. (8.12)

12.18 Members of the Release Committee should have expert knowledge of genetic engineering techniques, microbiology, theoretical or field ecology or other relevant disciplines. They should be drawn from universities, other institutions, industry and workers' representatives. Persons engaged in the development and release of genetically engineered organisms should not be debarred from membership of the Committee but interests should be declared appropriately. Experts from the UK and from other countries should be invited to join the Committee on an *ad hoc* basis when needed for the assessment of particular proposals. There should also be representation from relevant Government departments and agencies and from local authority environmental health officers. (8.13)

12.19 In addition to advising on proposals for release, including any conditions which should be attached to licences, the Release Committee should have other functions including: development of codes of practice and guidance for applicants; advising on the scope for categorising releases; advising on the need for research especially on matters relating to release; reviewing the outcomes of releases; liaising with overseas organisations in relevant fields; and advising on possible needs for changes in legislation or procedures. The Committee should be asked to produce an annual report on its activities, on developments in the subject and on lessons learned. Adequate resources should be provided for its effective operation. (8.15)

12.20 The functions of the Department of the Environment's Interim Advisory Committee on Introductions (IACI) should be taken on by the Release Committee, so that there will be no continuing need for IACI. (8.16)

12.21 The Secretary of State for the Environment and the HSC, acting on advice from the Release Committee, should compile and maintain a register of persons authorised to release GEOs. It would be an offence for a person not so registered to be responsible for carrying out a trial release. A registered person would be held personally responsible by the registration authorities for the use of appropriately qualified and trained staff for every aspect of the release and for the issuing of adequate instructions for them. He or she should be required to record the names of all staff engaged in the release and to make the names available to the registration authorities if requested. (8.17)

12.22 Appropriate arrangements should be made for the registration of companies or other organisations which carry out trial releases. Criteria for their entry to the register should include the employment of suitably qualified personnel, the provision of appropriate training, designation of safety officers and the establishment of a local safety assessment committee. Registered organisations should be required to identify one or more registered persons who would be responsible for releases. (8.17)

12.23 Registration, either of persons or of organisations, could be made in respect of a single release, a specified series of releases or any release of a specified class or classes of organism. In addition to trial releases, it might occasionally be appropriate to require the registration of releasers of a licensed product; provision for this should be made in the legislation. (8.18)

12.24 The new legislation should provide that any person, or the directors of any company or other organisation, responsible for carrying out the release of a genetically engineered organism without the necessary licence and registration, will be subject to strict liability for any damage arising. It should also

provide that neither the licensing and registration authorities, nor members of the Committee on whose advice they or either of them acted in granting the licence or registration, should be liable in respect of the consequences of the release. (8.19)

12.25 The Secretary of State for the Environment should have the power to impose, in the release licence, a condition that the licence holder monitors the spread and fate of the organisms and of any introduced genes, the environmental impact of the release and any unexpected ecological event. The licence holder should be required to report the results of the monitoring to the licensing authorities, with immediate reporting of any significant untoward occurrence. There should be provision for monitoring to be required, on a temporary basis, in the case of licensed products where necessary. (8.20)

12.26 There should be a public register of applications for release licences and of licences granted. This should contain the names and addresses of the persons or organisations making the applications, particulars of the organisms, the purposes of the releases and descriptions of the release sites. The register should be maintained nationally. Relevant sections of it should be kept in the localities of releases. (8.23)

12.27 Information about releases of GEOs, concerning foreseeable effects and arrangements for monitoring and dealing with emergencies, should be made available by the DOE or the HSE on request. (8.23)

12.28 The national register should contain details of applications and licences granted for the sale or supply of GEOs as or in products. The register of authorised releasers should also be made public. (8.23)

12.29 Persons or organisations applying for licences to carry out trial releases of GEOs should be required to place advertisements, in the local press serving the areas of intended releases, announcing their proposals. Anyone applying for a licence for the sale or supply of a GEO as or in a product should be required to place a notice in the London Gazette and an advertisement in an appropriate national newspaper. (8.24)

12.30 The legislation should empower the licensing authorities to allow public access to the information on the basis of which the Release Committee has made its recommendation. It should also enable them, if they considered it appropriate before allowing access, to invite the applicant to comment on the request for information and to take account of the applicant's views on commercial confidentiality. (8.25)

12.31 The licensing authorities will need to be able to communicate information about release proposals to the European Commission and competent authorities in other EC member states and other countries; if a specific power is necessary for that, it should be given to them. The UK authorities should also, if necessary, be empowered to make information available to the OECD, UNEP and other international organisations, and should do so to the fullest extent possible. (8.26)

12.32 Members of the public should have the opportunity to make representations to the licensing authorities in respect of any application for a release licence within 30 days of the appearance of the local or national advertisement. The applicant, and anyone who has made such representations, should subsequently receive a copy of the recommendation made by the Release Committee and be given the opportunity to make representations

about that recommendation before the decision of the licensing authorities is taken. (8.27)

12.33 The powers over the release of genetically engineered organisms which are to be exercised by the Secretary of State for the Environment and the HSC should apply to the marine environment within UK territorial waters. They should exercise these powers in consultation with the Minister responsible for fisheries. (8.28)

12.34 There will need to be an extension of controls over contained work on genetically engineered organisms to minimise the risk of damage to the environment. These will include powers to require the proper disposal of waste products and to regulate storage, transport and import for contained use. The powers should be given to the Ministers already having responsibilities in each area. (8.29)

12.35 The Secretary of State for the Environment should be given power in respect of waste disposal from contained work on genetically engineered organisms. In exercising his power, including the issue of advice by Her Majesty's Inspectorate of Pollution to the waste disposal authorities immediately responsible, he should receive advice from the ACGM and, as appropriate, from the Release Committee and elsewhere. (8.29)

12.36 The Secretary of State for the Environment, together with agriculture and other Ministers, should conduct a review of issues arising over the selection and use of naturally occurring organisms. They should consider the possibility of enacting more comprehensive controls than those afforded by the Wildlife and Countryside Act and other present legislation. (8.30)

Recommendations other than for the regulation of release

12.37 It is important that any definition of genetic engineering should be kept under review by experts and amended as necessary both to clarify if necessary the position of new techniques and to modify the coverage in the light of experience. (2.16)

12.38 International measures are called for in relation to commercial releases of plants. Viable samples of current commercially-used plant varieties should be conserved so that it will be possible to return to these in order to eliminate an undesirable trait if necessary. There should be lineage registers which record the history of plant varieties including information on any introduced genes. In addition, before organisms with introduced genes are released the introduced DNA sequence for the new genes should be characterised for future reference. (5.41)

12.39 Research on selective, readily degradable chemical pesticides leaving no objectionable residues and which are non-toxic to humans should not be abandoned in the enthusiasm for biological control. The development of agricultural practices such as integrated pest management, which may help to reduce the scale of the problem with which pesticides are trying to deal, should also continue to receive attention. (5.48)

12.40 Local safety assessment committees may not need the same range of expertise as the national committee but should contain ecologists as well as experts in genetic engineering. Other members with relevant local knowledge and expertise should be appointed where possible. (6.10)

12.41 Local authority environmental health officers should be invited to serve on local safety assessment committees. In order to make an informed

contribution on a subject which is somewhat outside the range of current EHO responsibilities, training and advice will be needed. (6.10)

12.42 It is clearly desirable that there should be international agreement on the information to be required of releasers and the procedures for assessment. We hope that the Government will use the final version of the ACGM's revised guidelines for information and risk assessment as a model in international discussions on this subject. (6.12)

12.43 The progression from laboratory to widespread release should go through a series of stages gradually relaxing the degree of containment at each, for example from laboratory, to greenhouse, to single field trial, to wider trials, to full marketing. (6.23)

12.44 As products move through stages of release, responsibility for scrutiny may fall progressively to various bodies. Close links are needed between these bodies together with arrangements for exchange of information about assessments and about the results of releases that have taken place. (6.23)

12.45 There should be a step-by-step approach to innovation in the releases that take place so that the modifications made at each step do not introduce an unacceptable degree of uncertainty. (6.24)

12.46 The use of debilitating mechanisms should always be considered when genetically engineered micro-organisms are proposed for release. (6.27)

12.47 The potential for clean-up and decontamination of a release site should always be considered but it would nevertheless be prudent to work on the assumption that, once released, it may not be possible totally to eradicate an organism, particularly a micro-organism, from the environment. (6.29)

12.48 Releasers should be given clear advice by the Release Committee, both in general guidance on good practice and in specific comments on their releases, about the manner in which releases should be carried out, including arrangements for security, for monitoring, for clean-up and for dealing with contingencies. Compliance with these arrangements should be checked by appropriately trained inspectors with authority to take action where necessary. (6.31)

12.49 At least until more knowledge is gained and confidence acquired about the behaviour of GEOs in the environment, releasers should be required to carry out monitoring. (6.32) When assessing a proposal, the Release Committee should consider the extent, methods and arrangements for the monitoring that should be carried out. (6.33)

12.50 The monitoring of the release of a GEO should normally continue after completion of the experiment for an appropriate period depending on the nature of the release, with agreed arrangements for reporting the outcome. (6.34)

12.51 There is scope for co-ordinating the general monitoring of the environment to develop a systematic approach. The DOE should take the lead in promoting and funding this co-ordination work as part of its responsibilities for the protection of the environment. (6.42)

12.52 The Release Committee should carry out regular reviews of the information it has obtained about the outcome of releases. Consideration should be given to publishing the results of the reviews. (6.46)

12.53 International exchanges of information between assessment bodies could provide valuable material to assist in assessing release proposals. The European Commission has proposed regular exchanges of information on this subject between member states. We support this initiative. (6.47)

12.54 We recommend that the UK authorities should, in appropriate circumstances, notify proposed releases of GEOs to the competent authorities not only in other EC member states but also in other countries and should take full account of their views. (9.22)

12.55 The relationship between living organisms and their environment is such that proposed releases of GEOs must be considered in the appropriate environmental context. This aspect of the draft EC Directive on the release of GEOs needs further thought and should be the subject of careful discussion between the European Commission and member states. (9.25)

12.56 The list of exclusions from the products section of the draft EC Directive on the release of GEOs considerably weakens the value of the proposals. Where product controls exist, those responsible for them must, before they authorise release of a product which is or which contains a genetically engineered organism, receive expert advice on those features which differentiate it from, for example, a chemical product. For products which are subject to no control, it is essential that controls should be established in respect of those which are or which contain GEOs. (9.26)

12.57 We support proposals by the European Commission for regular meetings of officials from member states to discuss and exchange information on release proposals, for an expanded research programme on biotechnology, in particular on risk assessment of releases, and for the creation of a database of releases. (9.29)

12.58 The ACGM, in consultation with the Release Committee, HSE, DOE and MAFF, should revise its containment guidelines to take into account potential harm to the environment from the escape of GEOs. (10.4)

12.59 The risk of accidents in the use or storage of commercially produced GEOs needs to be considered when proposals for products which are or which contain GEOs are put forward for assessment. Clear labelling, including instructions for storage, use, disposal and action to be taken in the event of an accident, should be considered where potential hazards exist. (10.6)

12.60 Well-designed protocols for procedures at the laboratory, field trial site and production process plant are very important in reducing the risk of accidents occurring. Staff should be appropriately trained so that they understand how to handle the GEOs and associated equipment safely. Response plans should be drawn up to deal with the consequences of an accident and staff should be trained to implement them. (10.7)

12.61 Her Majesty's Inspectorate of Pollution should consider the waste disposal issues raised by the development of genetic engineering techniques and, in consultation with the appropriate authorities, issue advice on the selection of BPEOs for the disposal of the wastes. (10.9)

12.62 When a proposed product which is or which contains a GEO is submitted for assessment, a licence should be granted only if any waste or residue can be disposed of safely and if appropriate advice on waste disposal appears on the product label. (10.10)

12.63 Guidance for the disposal of GEOs in biological and biotechnological waste, and its enforcement, should be kept under review to ensure that it remains appropriate. The waste disposal procedures recommended for field trials should also be kept under review. (10.10)

12.64 We have recommended a degree of public access to information about releases which goes beyond the access allowed in respect of most products. Some of this information could be of value to other companies. (10.11) A regime of intellectual property rights should be developed which provides sufficient protection to enable the release of adequate information to the public without undermining the commercial viability of the development and thereby damaging the incentive for innovation. (10.19)

12.65 Knowledge of genetics and ecology should be included in the curriculum in schools. Students should be aware of the factors involved in judging the impact on the environment of a proposed release. (10.21)

12.66 There is a need for a substantially enhanced research base in the basic sciences underpinning the release of genetically engineered organisms to the environment. (10.28) It should be located in the universities and research institutes and should receive adequate funding. Such research should be in three major areas: the molecular biology of organisms in the environment, interactions between organisms and the environment and basic studies on ecology and population biology. (10.29)

12.67 Basic research should be supplemented by projects related to specific environmental issues commissioned by the relevant Government departments. (10.30)

Acknowledgement

In carrying out this study we have been particularly grateful to our consultants, Professors John Beringer, Dick Flavell and John Lawton, Dr Yvonne Cripps and Dr David Tyrrell. Their help in guiding us through this rapidly developing subject has been invaluable. We are also indebted to all those who gave evidence and helped us in other ways. We have listed them in Appendix 2 and offer apologies as well as thanks to any we may have inadvertently overlooked. As ever we have been ably supported by our small secretariat and would particularly like to thank Joyce Bent and her word processor for coping so quickly and so patiently with the typing and retyping of the various drafts.

ALL OF WHICH WE HUMBLY SUBMIT FOR YOUR MAJESTY'S GRACIOUS CONSIDERATION

Lewis (Chairman)
Cranbrook
Nathan
Barbara Clayton
Henry Charnock
Gordon Conway
Lancelot Gilling
David Newland
Jeremy Pope
Emma Rothschild
Aubrey Silberston
William Stewart
Charles Suckling
Martin Vessey

B Glicksman — Secretary

P S Dale, M R Davies — Assistant Secretaries

June 1989

One of our members, Mr John Edmonds, was unable to take part in our deliberations because of his other commitments. In the circumstances he decided that he could not properly sign this Report.

APPENDIX 1

Members of the Commission and consultants during the period of study leading to the present Report

Chairman

THE RT HON THE LORD LEWIS OF NEWNHAM, Kt, MA, MSc, PhD, DSc, ScD, CChem, FRSC, FRS
Professor of Inorganic Chemistry, University of Cambridge
Warden of Robinson College, Cambridge
Past-President, Royal Society of Chemistry

Members

PROFESSOR H CHARNOCK, MSc, DIC, FRS
Emeritus Professor of Physical Oceanography, University of Southampton
Chairman, Meteorological Research Sub-Committee, Meteorological Committee

PROFESSOR DAME BARBARA CLAYTON, CBE, MD, PhD, Hon DSc(Edin), FRCP, FRCPE, FRCPath
Honorary Research Professor in Metabolism, University of Southampton
Chairman, Committee on Medical Aspects of the Contamination of Air, Soil and Water
Deputy Chairman, Department of Health Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Chairman, Standing Committee on Postgraduate Medical Education
Honorary Member, British Paediatric Association

*PROFESSOR G R CONWAY, PhD, DipAgricSci, DTA, FIBiol
Professor of Environmental Technology, University of London
Director, Centre for Environmental Technology, Imperial College of Science and Technology (1976–86)
Director, Sustainable Agriculture Programme, International Institute for Environment and Development

THE RT HON THE EARL OF CRANBROOK, MA, PhD, DL, FLS, FRSA, FIBiol
Board Member, Anglian Water Authority
Board Member, Institute for European Environmental Policy
Member, Natural Environment Research Council (1982–88)
Vice-President, National Society for Clean Air

MR L C G GILLING, OBE, BSc, FIBiol, FRAgs
Member, Minister of Agriculture, Fisheries and Food's Northern Regional Panel (1982–88)
Chairman, Executive Committee, Yorkshire Agricultural Society
Life Vice-President, Yorkshire Philosophical Society
Vice-Chairman, Yorkshire Museum Committee
Principal, Askham Bryan College of Agriculture and Horticulture (1957–84)

* Professor Conway resigned from the Royal Commission on 1 January 1989 to take up the post of Representative of the Ford Foundation for India, Nepal and Sri Lanka.

THE RT HON LORD NATHAN, MA, LLD(Hon), FSA, FRSA, FRGS
Solicitor/Consultant, Denton, Hall, Burgin & Warrens, Solicitors
Senior Partner, Herbert Oppenheimer, Nathan & Vandyk to 1986
President, UK Environmental Law Association
President, National Society for Clean Air
Member, House of Lords Select Committee on European Communities (1983–88) and Chairman of its Environment Sub-Committee (1983–87)
Chairman, House of Lords Select Committee on Murder and Life Imprisonment

PROFESSOR D E NEWLAND, MA, ScD, FEng, FIMechE, FIEE
Professor of Engineering, University of Cambridge
Fellow of Selwyn College
Consulting Engineer
Former Member, Council of the Fellowship of Engineering

MR J J R POPE, OBE, MA, FRSA
Deputy Chairman and Managing Director, Eldridge, Pope and Co. plc (Brewers and Wine Merchants)
Chairman, The Winterbourne Hospital plc
Deputy-President, Food and Drinks Federation
Member, Top Salary Review Body

EMMA ROTHSCHILD, MA
Senior Research Fellow, King's College, Cambridge
Associate Professor of Science, Technology and Society, Massachusetts Institute of Technology (1978–88)
Member, OECD Group of Experts on Science and Technology in the New Socio-Economic Context (1976–80)
OECD Science Policy Examiner, Australia (1984–85)
Board Member, Stockholm International Peace Research Institute

PROFESSOR Z A SILBERSTON, CBE, MA
Professor Emeritus of Economics, University of London
Senior Research Fellow, Imperial College of Science, Technology and Medicine
Secretary-General, Royal Economic Society
Member, Restrictive Practices Court
President, Confederation of European Economic Associations

PROFESSOR W D P STEWART, BSc, PhD, DSc, FIBiol, FRS, FRSE
Secretary and Deputy Chairman, Agricultural and Food Research Council
Boyd-Baxter Professor of Biology, University of Dundee
Past-President, Scottish Marine Biological Association
Vice-President, Freshwater Biological Association
Past-Chairman, International Committee on Microbial Ecology
Member, Advisory Board for the Research Councils
Past-Member, Natural Environment Research Council

DR C W SUCKLING, CBE, PhD, DSc, DUniv, CChem, FRSC, FRS
Consultant in science, technology and innovation
Member, Electricity Supply Research Council
Treasurer, Council of the Royal College of Art

Professor M P Vessey, MA, MD, FRCP, FFCM, FRCGP
Professor of Social and Community Medicine, University of Oxford
Fellow, St Cross College, Oxford
Chairman, Department of Health Advisory Committee on Breast Cancer Screening
Adviser, Special Programme on Human Reproduction, WHO
Member, Committee on Safety of Medicines

Consultants

Professor J E Beringer BSc, PhD, FIBiol
Head of Department of Microbiology, University of Bristol
Chairman, ACGM Intentional Introduction Sub-Committee
Member, Science and Engineering Research Council, Plant Science and Microbiology Committee
Member, Natural Environment Research Council, Terrestrial Life Sciences Committee

Dr Yvonne Cripps LLB(Hons) LLM, PhD
Fellow, Tutor and Director of Studies in Law, Emmanuel College, Cambridge
Visiting Professor of Law, Cornell University, New York
Editor, Biotechnology Law Report
Member, Cambridge Medical Ethics Forum

Professor R B Flavell BSc, PhD
Director, John Innes Institute, Norwich
Director, International Society for Molecular Plant Biology
Member, Scientific Advisory Board of CIAT (an international institute concerned with tropical agriculture in Columbia)

Professor J H Lawton BSc, PhD, FRS
Director, Centre for Population Biology, Imperial College, Silwood Park
Professor of Community Ecology, Imperial College of Science, Technology and Medicine
Member, British Ecological Society
Member, American Society of Naturalists

Dr D A J Tyrrell CBE, MB, ChB(Hons), MD, MRCP(Lond), FRCP (Lond), MRCPath, FRCPath, FRS
Director, MRC Common Cold Unit, Salisbury
Chairman, Advisory Committee on Dangerous Pathogens
Chairman, Joint Working Party, Royal College of Physicians and Royal College of Pathologists on Infectious Diseases
Member, WHO Expert Advisory Panel on Virus Diseases

APPENDIX 2

Organisations and Individuals Contributing to the Study

Listed below are those organisations and individuals who gave written evidence or assisted the Commission in other ways during this study. Those marked * gave oral evidence at formal Commission meetings; those marked + gave oral evidence during visits by the Commission, details of which are listed at the end of this appendix.

Government Departments

Department of the Environment*
Department of Health and Social Security*
Department of Trade and Industry, including
    Laboratory of the Government Chemist*
    Patent Office
    Warren Spring Laboratory
Foreign and Commonwealth Office, including several overseas posts
Home Office
Ministry of Agriculture, Fisheries and Food*
Ministry of Defence
Scottish Development Department
Scottish Home and Health Department

Other Organisations

Agricultural and Food Research Council
Agricultural Genetics Company Ltd*
Association of the British Pharmaceutical Industry
Association of Metropolitan Authorities

Bio-Information (International) Ltd
British Crop Protection Council
British Ecological Society
British Trust for Ornithology

Commission of the European Communities+
Confederation of British Industry
Council for Science and Society

Economic and Social Research Council

Fauna and Flora Preservation Society
Forestry Commission

Green Alliance*

Health and Safety Commission*
Health and Safety Executive*, including
    Advisory Committee on Genetic Manipulation*

Imperial Chemical Industries plc* +
Institute of Biology
Institute of European Environmental Policy

Medical Research Council
Microbial Resources Ltd
Monsanto plc*

Nature Conservancy Council* +
Natural Environment Research Council, including
    Freshwater Biological Association+
    Institute of Virology*
Nickerson Seed Company Ltd

Organisation for Economic Co-operation and Development

Public Health Laboratory Service, including
    Centre for Applied Microbiology*

Royal Environmental Health Institute of Scotland
Royal Society for the Prevention of Cruelty to Animals

Scottish River Purification Boards' Association

UK Genetics Forum
University of East Anglia

Water Authorities Association
Water Research Centre
Wildlife Link

Individuals

Professor T Atkinson	(Public Health Laboratory Service)*
Professor D Baltimore	(Whitehead Institute for Biomedical Research, Cambridge, Massachusetts)
Professor J E Banatvala	(United Medical and Dental Schools of Guy's and St Thomas' Hospitals)*
Professor R J Berry	(University College, London)
Dr S Brenner	(MRC Molecular Genetics Unit, Cambridge)
Professor D M Broom	(University of Cambridge)*
Dr F Brown	(Wellcome Research Laboratory)*
Dr N J Byrne	(University of London)
Professor G Dworkin	(University of London)
Mr J Elkington	(formerly of Earth Life Foundation)
Dr L V Giddings	(formerly of US Congress Office of Technology Assessment, USA)*
Professor J L Harper	(University College of North Wales, Bangor)
Dr D Kingsbury	(National Science Foundation, USA)*
Professor P J Lachmann	(University of Cambridge)*
Professor R M May	(University of Oxford)
Dr S Primrose	(Amersham International plc)
Mr J Rifkin	(Foundation on Economic Trends, USA)*

Mr S Shackley	(Science Policy Research Unit, University of Sussex)
Professor R A Weiss	(The Institute of Cancer Research, Royal Cancer Hospital)
Professor M H Williamson	(University of York)
Professor A J Zuckerman	(London School of Hygiene and Tropical Medicine)*

Visits

During the course of this study Members of the Commission visited the organisations listed below:

3 February 1988:	Plant Breeding Institute, Trumpington, Cambridgeshire
3 June 1988:	Imperial Chemical Industries (Plant Protection Division), Jealott's Hill, Bracknell, Berkshire
23–24 June 1988:	Commission of the European Communities, Brussels, Belgium

APPENDIX 3

The Commission's Invitation for Evidence, July 1986

The Royal Commission, under its new Chairman Sir Jack Lewis, has decided that it should undertake three studies over the next year or so: the release of genetically engineered organisms into the environment; aspects of fresh water quality; and the application of the concept of Best Practicable Environmental Option which it has developed over the past few years.

I am writing to invite your organisation to submit evidence for the Royal Commission to consider in its study of the release of genetically engineered organisms to the environment. In this study the Commission will include all organisms: animal, plant and micro-organisms.

This study is being undertaken because the Commission feels that it has a special responsibility, to Parliament and the public, to make an objective assessment of an issue which is likely to be of growing public concern. By making a timely contribution to public debate, the Commission hopes that its advice will assist the evolution of effective guidelines and controls both in this country and in the European Community. In the course of its study the Commission will examine broad issues such as the risks which could accrue from the environmental use of genetically engineered organisms in the context of the potential benefits; whether current guidelines or regulations are adequate to ensure good practice both in experimental releases and in subsequent use of genetically engineered organisms in the environment, particularly with respect to monitoring the dispersion and control of such organisms.

In addition to these broad issues the Commission has identified some questions which it expects to address; these are attached as Annex A.

While this letter and its Annex may indicate the aspects of this important topic that have already been identified they are not an exhaustive list of relevant issues and I stress that the Commission would welcome evidence from you on other questions about this subject that you feel should be drawn to its attention.

In preparing your evidence you may feel able to draw attention to published or readily available material that the Commission would find useful; and it would be of great help to both the Commission and its Secretariat if such material could be identified swiftly, while preparation of special submissions with the opinions of your organisation could take longer. In any event the Commission would be grateful if evidence could be submitted before 31 October 1986.

Evidence and all other communications should be addressed to the Secretary at the above address. It would be of great assistance to the Commission in planning its business over the next few months, if you were able to let me know at an early date whether or not your organisation proposes to submit evidence; and if it is your intention to do so, the date when the Commission can expect to receive it and the subjects likely to be covered.

Signed by the Secretary to the Commission

ANNEX A

RCEP Study on the Release of Genetically Engineered Organisms to the Environment

1. The study will distinguish, if possible, between:

   (a) genetically engineered organisms: organisms in which either their DNA has been deliberately modified by using recombinant DNA (rDNA) methods, or genetic information has been exchanged across species by techniques such as cell fusion, transformation, transduction, transfection, conjugation, micro-injection and micro-encapsulation

   (b) genetic selection: for example by conventional breeding and selection techniques such as cross pollination of crop plants, or by mutation and selection as with micro-organisms and

   (c) natural selection during the course of evolution.

2. Are there — ecologically, environmentally or ethically — any significant differences between releasing the products of 1(a) and 1(b), or indeed between releasing these products and releasing exotic organisms obtained by natural selection and released into a new environment, or releasing unnatural concentrations of such organisms?

3. To what extent can replication of rDNA organisms in pre-release studies really predict replication patterns after release into the environment? Is the risk of disrupting ecological systems greater with those organisms than with the release of exotic or high concentrations of naturally selected organisms?

4. If an organism performs differently from expectation and disrupts the environment adversely can its control or destruction always be ensured? Is release justifiable if control cannot be achieved?

5. Is the existing legislative framework governing the release of genetically engineered organisms adequate? If not, what changes are desirable and practicable?

6. Should the same rules/guidelines be applied for all releases, or is it possible to differentiate on the basis of scale, environment or the type of organism released? Should there be different regulations and controlling authorities for different uses of released organisms e.g. agriculture or medicine?

7. Is the present practice of case by case review likely to be overwhelmed by an increase in numbers of applications for permission to release engineered organisms? If the present practice becomes unworkable what should be put in its place?

8. How best can the need for public education in both the potential benefits and the potential risks of released genetically engineered organisms in the context of alternative actions be satisfied? What information about specific releases should the public have ready access to?

9. Ownership and responsibility: who should bear the costs of damage attributed to released organisms?

APPENDIX 4

Viruses

Structure

1. Outside their host cell, viruses are inactive particles composed of nucleic acid (either RNA or DNA), proteins and other chemicals. They range in size from small loops of naked RNA, called viroids, to objects as large as a small bacterium. The total number of bases in a virus is usually about 10,000 or less and the whole genome sequence is known for some of them.

Biology

2. Viruses are found in many different orders of the living world, such as bacteria, plants, insects, birds and mammals including man. This section describes some of their basic biology which is relevant to their genetic behaviour.

Replication

3. The mechanisms of replication for the various sorts of RNA and DNA viruses are very different but in all cases they need access to the appropriate host organism's cells. Having come near the cell, the virus attaches to it and enters. Its protein coat is removed so that the nucleic acid is released and becomes active, often with the aid of a virus enzyme. The virus uses the replicative machinery of the cell to produce many copies of its genome and proteins. These are assembled to form particles containing nucleic acid surrounded by a protective protein coat which are then spread either within the host organism or into the environment by a variety of mechanisms. Viruses in cells act as separate genetic entities mutating, being selected and evolving. Scientists are just starting to learn how viral genes are switched on and off and the ways in which viral products function in cells. For example, the same viral genetic sequence can be used to direct the synthesis of two or more proteins by being read in the alternative reading frames. Viral gene products are classified into structural or non-structural and are as varied in their different ways as the mechanisms of nucleic acid replication.

Viral genetic change

4. This can occur by mutation (including nucleotide substitution, deletion or addition). Occasionally, as will be described in the sections on host specificity and genetic exchange in this appendix, viruses can recombine or reassort obtaining genetic material from other, usually closely related, viruses. There is even some evidence that some viruses may evolve by duplicating genes. It is interesting to note that viral RNA in the cell is not subject to the forms of mutational repair experienced by DNA in most DNA viruses and in other organisms containing chromosomal DNA. RNA viruses can mutate and evolve rapidly, partly because of this relatively inaccurate copying mechanism.

The potential for the exchange of genetic material

5. There is evidence that in nature viruses may, to a limited extent, exchange genetic material with related viruses, but for this to happen they must be infecting the same cell. The frequency depends on several factors including the type of virus, its host range and its infectivity. For the exchange of genetic material to occur the viruses must have a similar gene structure and for the exchange to be significant the viruses must either have other unshared hosts

and/or function differently after the exchange. The system of replication used by viruses often prevents them acquiring additional genetic material but some large viruses, such as vaccinia, can incorporate small amounts of additional material under laboratory conditions.

6. Laboratory studies, and to a limited extent observation of nature, have shown that the potential for the exchange of genetic material varies between different types of virus. In general, single stranded RNA viruses such as Rhabdoviruses, Flaviviruses, and Togaviruses, do not exchange genetic material; but some, such as Picornaviruses and Coronaviruses, can. Exchange can occur more freely between closely related RNA viruses with segmented genomes such as Orthomyxoviruses, Reoviruses and certain plant viruses. The exchange occurs between sequences which code for the same function in the two viruses. DNA viruses can exchange material with other genetically compatible viruses and with the genome of the host, perhaps through the use of transposons. The transfer of genetic material from a recombinant DNA virus into the genome of an animal host would not affect a whole population unless germ-line cells were involved. In bacteria, however, all the cells are germ-line and integrated, bacterial viral nucleic acid is inherited by all progeny cells.

Host specificity

7. Host range is determined to a great extent by the envelope peptides of the virus. Most viruses are very host specific when tested in the laboratory and can be even more so in nature. Even so, the life cycle of a virus may involve widely differing species, often specific insects and mammals. In the virus life cycle there are two types of vector, those which transfer the virus mechanically and those which become infected and support replication. An example is the virus which gives man yellow fever, which replicates in an insect. Myxomatosis provides an example of an insect host passively spreading a viral disease of a mammal. Myxomatosis originates in rabbits in South America where it does not produce disease partly because the rabbits have evolved resistance to the virus. It has been introduced into both the UK and Australia to control rabbits but in the UK it is transmitted by fleas whereas in Australia it is spread by mosquitoes.

8. The influenza virus is a good example of a virus able to expand its host range. There are many types of influenza A virus which produce disease in birds, animals and man. The influenza virus has a segmented genome which means that there are opportunities for gene reassortment. For many types of the influenza virus this does not occur even when it is rife in one population which is in close contact with another. For example, fowl plague influenza can decimate poultry flocks without affecting the poultry farmers. Genes from the virus of one species can, however, be transferred to those of another, as can be seen in the infection of pigs by influenza virus with surface antigens of a human influenza virus after influenza epidemics have occurred in man.

Persistence and spread

9. Viruses can persist in the environment for varying lengths of time depending on the type of virus and the prevailing conditions. Studies of virus survival in water show that they are in general inactivated faster at higher temperatures, but this could be due to the increased activity of the aquatic flora and fauna and their enzyme products. Sunlight is important in the inactivation of viruses in water, as it often is more generally in the environment. Ice and snow shield viruses from the sunlight and extend their life expectancy. Turbidity is also important for virus survival both by filtering out sunlight and providing adsorption sites on particulates. The persistence of viruses in groundwater is not well studied or understood.

10. The study of the spread of foot-and-mouth disease provides interesting information on the spread of a virus. It is believed that foot-and-mouth disease virus can be spread short distances by animal to animal contact, contaminated food and water, and contaminated and inadequately disinfected accommodation. It can also spread long distances. An outbreak in the Isle of Wight was linked with one in Normandy, France by assuming that the virus was transported through the air in an aerosol plume and taking into account such factors as plume temperature, humidity, and exposure to ultra-violet light. The susceptibility to infection of certain animals by various routes of exposure to virus which had been deposited in the environment was also important.

Applications

Vaccination

11. Vaccination is currently the best method available to prevent and control viral infections, though for it to work well a good product and strategy for using it are required. Smallpox has been completely eliminated through a co-ordinated and carefully targeted world-wide scheme of vaccination and, as the disease is no longer present, vaccination against it is no longer necessary. Other diseases like poliomyelitis and measles can be controlled where vaccines are available but, as the viruses which cause these diseases are still present, the diseases can be prevented only by making sure that almost all the population are vaccinated. Vaccines are not only available for the control of viral disease in man but have also been used in animals both wild and domesticated. An example in wild animals is the attempt to control rabies in populations of susceptible wild animals by laying baits containing attenuated (or weakened) virus, to induce a protective immune response in the vaccinated animal. Scientists are currently testing a genetically engineered vaccine for rabies in which the gene that makes the protective protein of the virus is inserted into vaccinia virus, a vaccine vector which has many desirable properties for practical application (Appendix 5 paragraph 22).

Viral insecticides

12. Viral insecticides have been used for a number of years to control insect pests in the tropics and temperate countries. For example the baculoviruses of certain tree insect pests have been sprayed over millions of trees in Scotland for the last 10 years without any environmental problems arising or the pests developing resistance.

RETROVIRUSES

Structure

13. A retrovirus consists of 2 single-stranded RNA genomes wrapped in a core of viral protein which is surrounded by an envelope studded with viral glycoproteins derived from the cell membrane of the host cell. This structure, and the fact that the retrovirus needs a cell in which to replicate, makes it much like any other virus. The difference is that, when a retrovirus infects a cell, it brings with it an organised collection of viral enzymes and RNA designed to direct the synthesis of a double stranded DNA copy of its own genome (reverse transcription) and the integration of this DNA copy into the DNA of host chromosomes.

Replication

14. The retrovirus recognises and attaches itself to an appropriate host cell through the meshing of the proteins of the cell's surface and the virus envelope. The enveloped retroviral particle enters the cell and uncoats to form the nucleoprotein complex in which viral RNA is copied to DNA by

reverse transcriptase. The DNA copy of the retroviral genome migrates to the nucleus where it integrates into the host cell's chromosomal DNA. At this stage the retrovirus is dependent on the host cell to replicate and produce viral RNA and proteins. The new retroviral RNA genomes are packaged using virus coded material from the host cell's cytoplasm and then escape from the cell through the cell membrane.

Genetic behaviour

15. Because retroviruses are able to integrate their viral DNA stably into the chromosomes of somatic or germ cells and even to mutate or capture cellular genes, the genetic behaviour of retroviruses is of great interest. When more than one retrovirus infects a cell several types of genetic exchange can occur. The core proteins and genome of one virus can acquire envelope proteins from another which could change the type of host cells it is able to infect. The expression of the host genome may be affected either because the insertion of the viral genome disrupts genes which then do not function or because the virus genome stimulates host genes adjacent to the site of insertion. This activation of host genes by retroviruses can contribute to the development of cancer from infected cells.

Biological behaviour

16. The first retrovirus was isolated about 80 years ago making it among the earliest known types of virus. It was discovered as a filterable agent which caused cancer in chickens. Retroviruses have since been found in all the vertebrates that have been examined for them. They can be transmitted in the environment like all other viruses as inert particles protected by their protein envelope. Because on rare occasions they can integrate into the chromosome of germ line cells, however, they can also spread genetically from one generation to the next. On the other hand retroviruses may be produced in large amounts in a host organism but may not be infectious or produce disease.

Importance in genetic engineering

17. Retroviruses serve as a model for reverse transcription and a source of the enzyme reverse transcriptase, which is an essential tool in many types of genetic engineering.

18. Retroviruses are important in the study of the molecular basis of cancer. Some of them produce cancers in most types of laboratory animals: both quick developing tumours, such as that produced by the Rous sarcoma virus, and those that involve long latency periods and probably multistep processes, such as that produced by the mouse mammary tumour virus.

19. As is true of many other viruses, retroviruses can be excellent probes for elucidating the mechanisms of gene regulation and expression. They are also useful for understanding the interaction between the structure of the cell and its function, for example how the cell wall is crossed or how cells are recognised by viruses and bacteria.

20. It is hoped that retroviruses will provide powerful tools in the future for delivering genes in gene therapy and curing diseases. Experiments in many biological fields today depend on retroviral vectors genetically engineered in the laboratory to deliver genes to cultured cells and, occasionally, animals. However, there is still much to be learnt about how they integrate into the chromosome and control gene expression and about their overall safety before they will be acceptable for gene therapy.

Sources

1. H Varmus (1988) Retroviruses, Science 240 (4858) 1427–1435, 1988.
2. M Goddard, M Butler (Editors) (1980) Viruses and Wastewater Treatment. Proceedings of the International Symposium on Viruses and Wastewater Treatment. University of Surrey, Guildford, 15–17 September 1980. Pergamon Press.
3. Dr D A J Tyrrell. Evidence to the Royal Commission.
4. Professor R A Weiss. Evidence to the Royal Commission.

APPENDIX 5

Some Releases of Genetically Engineered Organisms

1. This appendix presents information about some of the releases of GEOs that have taken place, largely in the UK and USA. Two UK release programmes — those of the NERC Institute of Virology and the AFRC Institute of Plant Science Research, formerly the Plant Breeding Institute — are described in some detail, while others are referred to more briefly. The releases are considered in three categories: micro-organisms, plants and animals. Although only a few GEOs have been released, some tentative conclusions can be drawn about their reported impact on the environment and these are summarised in paragraphs 37–40.

MICRO-ORGANISMS

Field trials of genetically engineered baculovirus insecticides([21])

Purpose of field trial

2. This section describes a series of field trials undertaken by the Institute of Virology to develop a quick-acting viral insecticide and mechanisms for assessing the risks of releasing GEOs to the environment.

3. Baculoviruses have been used for decades in agriculture and forestry as biological pest control agents and have a good safety record. But, as with many biological pest control agents, the baculovirus takes several days to kill the pest because it has to go through several replication cycles to produce enough virus in the pest to kill it. The eventual aim of the programme is to engineer into the virus the ability to produce quicker-acting poisons, such as insect specific toxins from bacteria or scorpions, so that the pest is killed more quickly.

4. There were to be 4 field trials as part of the programme:

(a) The release of a genetically marked baculovirus, the nuclear polyhedrosis virus of *Autographa californica* (AcNPV). This took place in 1986.

(b) The release of a genetically marked and crippled AcNPV. The crippling involved removing the virus's protective protein coat which made it more susceptible to environmental degradation, particularly by ultraviolet light. This took place in 1987.

(c) In 1988 two releases were planned. The first was the release of the crippled virus again. The second involved releasing the crippled virus after inserting into it the bacterial gene for the production of beta-galactosidase. This gene enables bacteria to use the sugar lactose as a source of energy. The purpose of including this gene in the crippled AcNPV was to measure the level of expression of the beta-galactosidase in the caterpillar moths infected with the virus to check that the crippling of the virus had not affected its ability to express proteins.

5. This section will concentrate on the first two releases, for which results have been published.

Biology and genetic engineering of the baculoviruses

6. Baculoviruses infect specific members of the Lepidoptera (butterflies and moths) and Hymenoptera (wasps, bees, ants) families. Their genomes of DNA contain between 100,000 and 150,000 base pairs and are packaged in rod-shaped structures which are surrounded by one or more protein coats. In the AcNPV several of these coated viruses are embedded in a polyhedral inclusion body also made of protein.

7. The target of the virus in this study is the caterpillar of a particular moth, the small mottled willow (*Spodoptera exigua*). The caterpillars eat the virus with their food and break down the polyhedral inclusion body in their gut releasing the coated virus particles which penetrate and replicate in cells in the lining of the gut. Eventually the virus infection is sufficient to kill the caterpillars.

8. The virus is believed to be spread passively in the environment from the decaying bodies of the caterpillars by wind, rain splash and in the faeces of animals and birds which feed on the caterpillars. The virus's various protein coats enable it to survive in the environment, so it can persist from the autumn of one year to the spring of the next when the caterpillars become active again. The virus can survive in the soil and be carried above the surface on emerging plant seedlings.

9. Although some baculoviruses can acquire genetic material from their host species this is thought to be a very rare event. Any exchange of genetic material is most likely to occur during the co-infection of cells by related baculoviruses.

10. For the first release a marker piece of DNA, 80 base pairs long and synthesised in the laboratory, was added to the parent AcNPV just downstream from the gene which codes for the polyhedral inclusion body protein. The marker sequence was specifically designed not to contain any genetic sequences likely to affect the expression of other genes in the virus or its replication. In the case of the second release the gene which codes for the polyhedral inclusion body and its promoter were removed from the AcNPV and replaced by a different marker sequence of DNA of the same length. Again the added sequence did not contain any genetic material which could affect the expression of virus genes or its replication.

Pre-release testing

11. Three specific tests were made:

- The host range of the marked or crippled AcNPV was checked to ensure that it was the same as the original parent virus. At the request of the Nature Conservancy Council a large number of Lepidoptera, Hymenoptera, Neuroptera (alder, snake and lacewing flies), Diptera (two-winged flies), and Coleoptera (beetles) were tested to ensure that they could not be affected by the genetically altered virus. No difference was found between the host range of the genetically engineered and non-engineered parent virus, but much more of the crippled virus was required to kill the caterpillars that were susceptible to the virus.

- The genetic stability of the genetically engineered AcNPV was tested by breeding 50 generations of the virus. Checks made on the genetic material of the virus and its ability to infect susceptible caterpillars showed that the marker sequences were stable and did

not affect the ability of the virus to reproduce or produce proteins. In the case of the second release the crippled virus reproduced stably without making the polyhedral inclusion bodies.

— The ability of the virus to persist in the soil was determined using soil from the site where the field trial took place. The marked virus survived in the soil at 18°C for 14 days, retaining the same ability to infect susceptible caterpillars as its parent virus. The crippled virus was rapidly degraded in soil.

Field trial site

12. Both the field trials took place on the same site in open arable land at the Oxford University Field Station at Wytham, Oxfordshire. The flora and fauna at the site, particularly its butterfly and moth populations, were carefully studied before the release. The field trial was conducted in an enclosure (see Plate 10c) which was designed to be proof against insects, birds, small mammals (for example moles, rabbits) and large mammals (for example deer). In the course of the first field trial some beetles and spiders were found in the enclosure, probably having developed from eggs dormant in the soil; these were removed. Cabbage and sugar beet plants provided food for the caterpillars of the test species (*S. exigua*).

13. The night before the release the genetically engineered virus was fed in the laboratory to the test species caterpillars, *S.exigua*, so the virus was introduced by taking infected caterpillars to the field trial site. About 200 caterpillars were used in each trial.

Results of the first release

14. One week after the *S.exigua* caterpillars infected with the marked, genetically engineered virus had been introduced into the enclosure they had all died. Soil, cabbage and sugar beet plants, and chickweed (that had grown in the enclosure during the course of the experiment, presumably from seeds dormant in the soil or blown into it by the wind) were analysed for the engineered AcNPV. Virus was found on all the plants, including the chickweed, inside the enclosure but not on foliage sampled from plants growing outside the enclosure during the entire time the experiment was run. Virus was also found in the soil for the 6 months duration of the experiment. The marker sequence that had been genetically engineered into the virus was recovered intact throughout the sampling period. The virus was not found in a control population of uninfected *S.exigua* caterpillars which had been physically separated from the infected population in the enclosure. Plates 10a and 10b compare the damage the uninfected caterpillars did to the cabbages with the relatively undamaged cabbages exposed to the infected caterpillars.

Results of the second release

15. Again, one week after the *S.exigua* caterpillars infected with the marked, genetically engineered, crippled virus had been introduced into the enclosure they had all died. One week after this none of the debilitated virus could be found on the foliage of the plants, in the soil, or in the dead bodies of the infected caterpillars in the enclosure.

Site decontamination

16. At the end of each experiment the site was decontaminated using three treatments of a 5% formalin solution. The success of the decontamination was checked by challenging susceptible caterpillars with seedlings grown in soil samples from the site.

Public information activities

17. Permission to carry out the trials had been obtained from all the relevant Government authorities, including the MAFF, DOE, NCC and the ACGM, often after extensive discussion and the submission of further experimental evidence. Locally, the owners of the field site (Oxford University), senior University officials, the University Safety Officer, the Oxford HSE Factory Inspector, the Vale of White Horse Environmental Health Officer and the Environmental Services Committee of the Vale of White Horse District Council were all informed of the trials. Press releases were issued in national and local newspapers, radio and television interviews were undertaken and an environmental interest group was notified.

'Ice-minus' bacterium

18. Plant pathologists from the University of California, engaged in elucidating the mechanisms of plant frost damage, proposed to treat potatoes with a genetically engineered bacterium *Pseudomonas syringae* from which the gene for the ice-nucleation protein had been deleted. When this protein was produced by the bacteria it helped the formation of ice on plants causing frost damage. The engineered ice-minus bacteria were designed to reduce the risk of this happening by competing with ice-nucleating bacteria for available sites on the plants. Approval for the field trial, first sought in 1984, was given in May 1986. After extensive local consultation the trial was begun in April 1987 on a 0.5 acre site at the University field station in Northern California. The site was vandalised in May 1987. Apart from testing the ability of the ice-minus bacteria to protect the potatoes from frost, the mobility and persistence of the bacteria in the environment was also assessed. The United States Environmental Protection Agency (EPA) at the same time conducted experiments to evaluate their strategies for sampling and studying the air dispersal of genetically engineered micro-organisms released on a small field trial site. Some ice-minus bacteria were found in the fallow buffer zone around the trial site, but none were found on neighbouring vegetation or surface water. The bacteria persisted for about 1 week after spraying, in soil on the site. The results of the field trial bore out those obtained from contained laboratory and greenhouse experiments([140]).

19. Advanced Genetics Sciences Inc. (AGS) carried out trials of ice-minus bacteria on strawberry plants in California in 1987([141]).

Genetically marked soil bacterium

20. The purpose of the release was to test the efficiency of a particular marker for tracking the fate of a genetically engineered bacterium in the environment. The marker, genes from the bacterium *Escherichia coli* (*lac*ZY), were engineered into the bacterium *Pseudomonas aureofaciens*. After approval by the USA regulatory authorities the genetically engineered bacteria were released, in November 1987, on a 1 acre field trial site planted with wheat on the Clemson University Experimental Research Station in South Carolina. During the 18 month trial extensive monitoring of the site and the surrounding environment took place. Preliminary results showed the effectiveness of the *lac*ZY marker in tracking the engineered bacterium in the field. The genetically engineered *Pseudomonas* bacteria moved no further than 18cm from the wheat plants on the site. No marked bacteria were found in fallow buffer zones or surface water near the site. The behaviour of the marked bacteria corresponded well with results obtained from growth chamber experiments([142]).

Genetically marked nitrogen-fixing bacteria

21. The purpose of this experiment, by the Rothamsted Experimental Station, was to investigate the ability of nitrogen-fixing *Rhizobium* bacteria to

exchange genetic material and to survive in the soil, particularly between growing seasons. In 1987, after consulting the UK ACGM, an engineered *Rhizobium leguminosarum* bacterium was inoculated on plants in a field trial site in Hertfordshire. It contained a gene conferring resistance to the antibiotics neomycin and kanamycin, present on the Tn5 transposon of a transferable plasmid, and another gene in the chromosome conferring resistance to the antibiotics rifampicin and streptomycin. Experiments showed that the engineered bacteria did not nodulate the inoculated plants very well and that there was no evidence of the transposon being transferred to other bacteria. It is possible, however, that gene transfer would not have been detected because of the low levels of *Rhizobium* present on the site. Work done on a control plot with *Rhizobium* 'cicer' bacteria inoculated on *Cicer arietinum* suggested that the movement of *Rhizobium* through the soil was probably limited to 45–60 cm in a growing season. Experiments in 1988 were designed to test whether the engineered *Rhizobium* can survive from one growing season to the next to nodulate a variety of leguminous plants. This work is being undertaken in co-operation with researchers in France and Germany as part of the EC's Biotechnology Action Programme([143,144]).

Recombinant vaccinia-rabies vaccine

22. In Europe and elsewhere certain wild animals, especially foxes, provide a reservoir for the rabies virus which can kill man and many domestic animals. For some time now countries have attempted to vaccinate their wild animal populations to try to control the disease. A recent field trial in Belgium of a vaccinia vaccine, genetically engineered to induce an immune response to rabies, is the first stage in the development of a genetically engineered vaccine for this purpose. Before carrying out the trial the genetically engineered vaccine had been tested for safety on domestic, laboratory and wild animals. 250 chicken head baits containing the vaccine were distributed by hand over a 2.5 hectare study site on an isolated Belgian military base at a density of 40–50 baits per square km. 15 days after distribution about 64% of the baits had been eaten by wild animals. Wild animals trapped on the study site for 3 months after the bait was distributed showed no evidence of transmission of the vaccinia infection. Three boars killed on the site had no antirabies neutralising antibodies, but no foxes could be caught on the site during the 3 months the trial lasted. The small size of the trial makes it difficult to draw any firm conclusions except that the vaccine does not appear to pose a risk to wildlife or domesticated animals. A larger trial was due to start in the autumn of 1988. The release was controlled according to rules laid down by the World Health Organisation([71]).

PLANTS

The release of genetically marked potato plants([138])

Purpose of the field trial

23. A field trial of a genetically marked potato has been carried out by the Institute of Plant Science Research, Cambridge, UK, as part of a programme which supports the development and release of transgenic potatoes. Its purpose was to research the role of the patatin gene in the potato tuber and how its expression was regulated. The programme will examine:

- the introduction of genes into the potato which code for traits that will protect it from disease and certain environmental stresses;
- the development and testing of appropriate protocols to carry out releases of genetically engineered potatoes in field trials safely; and

— the success of the different plant culturing techniques used to produce genetically engineered plants in the field.

Biology and genetic engineering involved in the field trial

24. A common variety of potato, whose behaviour as an agricultural plant in the UK was well known, was used as the test plant for this trial.

25. The marker gene, neomycin phosphotransferase II (NPT II), is of bacterial origin and confers resistance to the antibiotics kanamycin and neomycin which are also of bacterial origin. To measure the way the patatin gene was regulated, a genetic construct was developed which attached the patatin promoter to a gene sequence from the bacteria *Escherichia coli* which codes for the enzyme beta-glucuronidase (GUS). There are simple biological assays that detect the amount of beta-glucuronidase present which could then be related to the strength of expression achieved by the patatin promoter.

26. Both GUS and NPT II are commonly found in soil microflora and in the mammalian digestive system. The GUS enzyme is not found in plants, however, although other enzymes of the glucuronidase group help to break down complex sugars in plants.

27. The genes for the kanamycin resistance marker and the production of the beta-glucuronidase enzyme were introduced into potato tuber tissue cells using *Agrobacterium tumefaciens* tumour inducing plasmids as vectors. This procedure is described briefly in paragraph 3.16 of this Report. Genes introduced in this way mostly incorporate at one site in the genome. Whole plants can be grown from these genetically engineered cells to produce transgenic potato plants that are kanamycin resistant and express beta-glucuronidase in a manner controlled by the patatin promoter gene.

Pre-release testing

28. The level and the stability of beta-glucuronidase was measured over several vegetative generations in the laboratory.

Field trial site and methods

29. The site of the field trial was a 30×50 metre plot at a distance of about 1 km from the nearest plot of potatoes on the Institute of Plant Science Research's field trial site in Cambridge. The trial was to last 2 years. In the first year about 2200 potato plants were planted, most of which were transgenic (Plate 9a). The plants were monitored for GUS activity, how they grew and whether they showed an increased disease susceptibility. Until the plants had grown a reasonable canopy of foliage they were weeded by hand.

30. During discussions with the ACGM before the trial took place there had been some concern expressed over whether the potatoes could have spread the added genetic material through natural cross-pollination, for example by bees. Natural cross-pollination between non-adjacent potato plants and the survival of seeds produced this way was believed to be rare. Nonetheless, all the transgenic potato plants were deflowered and deberried by hand during the trial to remove the risk of this happening (Plate 9b).

31. The second year of the trial involved growing the tubers produced by the transgenic plants used in the first year of the trial to check for the genetic stability of the added genetic material and whether it could be transferred to progeny that are produced vegetatively.

Decontamination of the site

32. The following procedures were adopted:

- All the potato plants were harvested at the end of the experiment and were destroyed (Plate 9c). The site was decontaminated by applying the herbicide glyphosate. If this proved unable to prevent the growth of plants from tubers which were left in the soil the whole site could be further decontaminated by fumigation with methyl bromide.
- After the end of the experiment the trial site would be followed up for at least the next year to ensure that any tubers left in the ground which germinated were destroyed.

Results of the field trial

33. The Institute of Plant Science Research are preparing a paper for publication later in 1989.

Public information activities

34. Besides obtaining approval from the ACGM for the field trial, the scientists at the Institute of Plant Science Research consulted their own local genetic manipulation safety committee, the Cambridge City Environmental Health Office, and the South Cambridge District Environmental Services Committee. The occasion of the release was accompanied by a Press Release and an article in the Cambridge Evening News.

Some other field trials of transgenic plants

35. Other examples of field trials of genetically engineered plants include the following:

- In 1986 Agracetus Corporation of the United States obtained approval to carry out a field trial of 200 tobacco plants which had been genetically engineered to provide resistance to the disease causing crown gall tumours. The release site was a 1/20 acre plot in Wisconsin([8]).
- In 1986 Rohm and Haas obtained permission for field trials in Florida and Mississippi of a tobacco plant that had been genetically engineered to incorporate a single gene from the bacterium *Bacillus thuringiensis*. This bacterium produces a toxin which kills particular leaf-eating caterpillars. The purpose of the engineering was to allow the plants to produce this toxin so that they would be protected from the caterpillars([8]).
- Monsanto, the company which produces the commonly used herbicide glyphosate, have identified a gene which confers resistance to the herbicide. After obtaining permission they conducted in the United States a field trial, in the summer of 1987, releasing tobacco, tomato and petunia plants engineered to incorporate the glyphosate resistance gene (introduced into the plants by the tumour inducing plasmid of the bacterium *Agrobacterium tumefaciens*)([8]).

ANIMALS

36. A variety of transgenic animals have recently been produced. They include the geep (a chimeric cross between a sheep and a goat)([145]), sheep that express in their milk a human protein which helps blood to clot([109]) and a mouse which is particularly susceptible to developing cancer of the breast([147]). None of these animals has been released, however, in terms of the definition of a release used in this Report (paragraph 2.17).

A DISCUSSION OF SOME OF THE COMMON ASPECTS OF THE RELEASES OF GEOs

37. This discussion of field trials involving the release of micro-organisms and plants may conveniently be divided into three main areas:

- pre-release testing and the management of field trials;
- experimental results; and
- the public response to the field trials.

Pre-release testing and field trial management

38. In the cases for which we have sufficient information:

- Extensive tests were carried out before the field trial to ensure that the GEO was genetically stable and host specific and that its likely environmental persistence and behaviour was reasonably well understood. In several cases discussions betweeen the releaser and the authorities approving the release resulted in modifications to the original release proposal or additional pre-release testing.
- The sites of the field trials were carefully chosen to be away from other crops, domesticated animals, surface water, and populated areas. Fallow strips generally bounded the trial sites and several experiments involved extensive analysis of environmental samples either for the GEO or the added foreign genetic material.
- At the end of the field trials the sites were decontaminated. Subsequent monitoring of the site has generally been undertaken to ensure that it has been successfully decontaminated.

Experimental results

39. Where there has been sufficient detail to permit an assessment of the results the following may be said:

- The GEO did not appear to display any characteristics that would not have been expected from the behaviour of the original organism in the environment and the genes engineered into it.
- The experiments did not appear to produce results other than those found for the GEO in contained laboratory and greenhouse testing, though this may merely reflect the fact that most of the GEOs released have been little different from their parent organisms.
- Micro-organisms did not appear to be particularly mobile in the environment and even when applied in an aerosol they were not detected as having spread far from the field trial site.

40. Few of the experiments have continued for more than one growing season so it is possible that the points made above will not be borne out by long term trials. Similarly, little can be said about the persistence of GEOs except where they have been deliberately engineered to be readily degraded, as in the case of the second Institute of Virology release (paragraph 15). Results from long term trials designed to monitor the environmental fate and persistence of GEOs and their foreign genes are awaited with interest.

Public response to the release of GEOs

41. This has varied markedly. In the USA most concern has centred around the release of genetically engineered micro-organisms, seemingly regardless of whether or not the releasers have attempted to describe to the public what

they are doing. Releases of transgenic plants have generally been met with little or no opposition. In the UK, where the ACGM has encouraged releasers to keep local authorities and the public informed about releases, there has been little or no public comment.

APPENDIX 6

GENHAZ Working Party

During the study a working party was set up to explore the feasibility of applying the risk identification technique known as HAZOP to the release of genetically engineered organisms (paragraph 6.17). The Commission would like to record its thanks to those who took part:

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GLOSSARY AND ACRONYMS

Glossary

Algae	Simple plants living in aquatic or moist habitats.
Amino acid	The chemical building block of proteins.
Antibiotic	A substance, produced by micro-organisms, that destroys or inhibits the growth of other micro-organisms.
Antibiotic resistance	The ability of an organism to grow in the presence of concentrations of an antibiotic that would otherwise kill it.
Attenuation	The process of reducing the virulence of micro-organisms by special treatment. Attenuated bacteria or viruses are used for some vaccines.
Bacteria	A diverse group of micro-organisms which do not have a nuclear membrane.
Cell	The structural and functional unit of all living organisms. In lower organisms cells exist as individuals or in colonies, whilst in animals and plants they are mainly organised into tissues.
Cell membrane	The semipermeable membrane forming the outer limit of the cell, which regulates the passage of materials in and out of the cell.
Chromosome	A large DNA molecular chain in the cell along which the genes are located.
Codon	A set of three consecutive nucleotide bases that specifies the insertion of a particular amino acid into a protein.
Coronaviruses	A group of viruses one of which causes avian bronchitis.
Cultivar	A cultivated variety of plant.
Differentiation	The change undergone by cells in which they alter their form and/or function.
DNA	Deoxyribonucleic acid, which is present in all living cells and contains the information for cellular structure, organisation and function.
Enzyme	A protein that changes the rate of, or promotes, a biological reaction.
Escherichia coli	A species of bacterium living in the gut of man and certain other vertebrates, which is normally non-pathogenic. It is involved in the digestion of particular sugars.
Evolution	The change in genetic make-up of a population with time.
Expression	The process of producing proteins using the information contained in genes.

Flaviviruses	A group of viruses commonly transmitted by arthropods (for example certain insects) between vertebrates. One member causes yellow fever in man.
Foreign genes	Specific gene sequences from one organism that are introduced into another organism.
Fungi	Unicellular or filamentous organisms lacking chlorophyll. Fungi constitute a separate kingdom of living organisms.
Gene	The unit of heredity, composed of DNA, which forms part of a chromosome. The genes code for particular proteins which are important in controlling the structure and function of cells.
Gene cloning	The production of many identical copies of a DNA sequence through propagation in bacteria, fungi or higher organisms.
Gene or genetic sequence	The order of nucleotide bases within the DNA. A sequence of bases could delineate a gene or represent a marker sequence.
Genetic mutation	A change in a base or bases of the DNA of an organism which results in an altered genetic characteristic. It can be caused by radiation, chemicals, or by genetic means.
Genome	All the DNA contained in a single set of chromosomes of an organism.
GEO	A genetically engineered organism (see paragraphs 2.12–2.14 of this Report).
Germ cells	Cells that divide to produce the sperm and eggs.
Hormone	A chemical messenger that is manufactured and secreted in an organism in small quantities to regulate specific biological processes elsewhere in the organism.
Immune system	The mechanism of an organism which combats infection by foreign, often disease-producing, organisms.
Incubation	Growth under controlled conditions of light, heat, humidity or nutrients.
Ligation	The joining together of DNA sequences.
Marker sequence	A sequence of nucleotide bases, engineered into the genetic material of an organism, used to trace a particular gene or organism.
Micro-injection	A technique used to insert nucleic acid directly into a host cell, usually via a very fine syringe.
Myxomatosis	A viral disease of rabbits. It has been used to control rabbit populations in the UK and Australia.
Naturally occurring organism	In this Report, includes any organism obtained, bred or selected by techniques not considered to be genetic engineering.
Nodule	A small, rounded swelling on particular plant roots, inhabited by nitrogen-fixing bacteria such as *Rhizobium*.
Nuclear membrane	A membrane forming the boundary of the nucleus in the cells of many organisms. It is permeable to certain substances and complexes of molecules.

Nucleic acid	Complex molecules found in cells. The two main types are DNA (deoxyribonucleic acid), which carries all the genetic information in chromosomes, and RNA (ribonucleic acid), which is a very similar molecule involved mainly in protein synthesis.
Nucleotide base	Nucleotide bases are strung along sugar-phosphate 'backbones' to form the nucleic acids DNA and RNA. DNA has four such bases: adenine, cytosine, guanine and thymine. In RNA uracil replaces thymine.
Nucleus	The body in cells in higher organisms which contains the chromosomes and is bound by a membrane.
Organism	Any living thing, including, for the purposes of this Report, a virus.
Orthomyxoviruses	Viruses which cause influenza in man and other animals.
Parasite	An organism which obtains its nutrients from and lives on or in another organism. The association does not necessarily result in the death of the host organism.
Pathogen	A disease-causing micro-organism.
Pest	An organism having a destructive association with another organism which might (but not necessarily) result in death. Such organisms are frequently an economic or medical nuisance to man.
Picornaviruses	A group of viruses, members of which cause diseases like the common cold and poliomyelitis in man, and foot-and-mouth disease in cattle.
Plasma	The liquid part of the blood containing dissolved substances important in bodily function.
Plasmid	A loop of DNA, in bacteria and certain other organisms, that exists and replicates independently of the chromosomes.
Protein	Proteins are the chemicals that control the function and structure of cells. Amino acids are strung together in chains to form proteins.
Protoplast	A plant cell which has had its cell wall removed.
Protoplast fusion	The joining together of the protoplasts of different cells within one cell membrane.
Recombinant DNA	DNA that has been modified by joining together different pieces of DNA using the techniques of genetic engineering rather than by traditional breeding methods.
Regulatory gene	A gene or combination of genes which controls the activity of other genes.
Reoviruses	A group of viruses found in the respiratory and intestinal tract of mammals and elsewhere in nature. They are not necessarily pathogenic.
Restriction enzymes	Enzymes produced by many bacteria which cleave foreign DNA in the bacteria. They are an important tool in genetic engineering for cutting DNA.

Rhabdoviruses	A group of viruses, one member of which causes rabies in vertebrates.
Rhizobium	A group of bacteria which forms an association with the roots of certain plants, enabling the plants to use nitrogen from the air to produce nutrients necessary for their growth.
RNA	A nucleic acid — ribonucleic acid — which is formed to translate the information contained in genes into the active chemicals, proteins. RNA can also be the hereditary material in certain viruses.
Saprophyte	A plant or micro-organism that feeds by absorbing organic material from dead organisms. Most fungi are saprophytes.
Somatic cells	All cells except germ cells. Mutations in somatic cells are not heritable.
Suicide gene	A gene, engineered into a GEO, whose function leads to the GEO's death in order to control and limit the GEO's survival in the environment.
Surface antigens	Receptors on the surface of cells that are recognised by antibodies.
Tissue	A collection of similar cells organised to carry out one or more particular functions.
Togaviruses	A group of viruses one member of which causes German measles in man.
Transcription	The first step in protein synthesis in which the sequences of DNA are copied into a form of RNA (called messenger RNA); this is subsequently translated, in structures in the cell (called ribosomes), to produce proteins.
Transposon	A mobile piece of genetic material.
Transgenic organism	An organism with a sequence of DNA from another organism genetically engineered into its genome.
Vaccination	The induction of immunity to disease by the administration of attenuated or inactivated viruses, or other organisms or their products in order to stimulate the production of a protective immune response.
Virus	A non-cellular particle composed of a protein shell and a nucleic acid core. It can reproduce only in living cells.
Weed	A plant growing in the wrong place.
Yeast	A group of unicellular fungi. Some yeasts are widely used in brewing and baking.

Acronyms

ACGM	Advisory Committee on Genetic Manipulation
AFRC	Agricultural and Food Research Council
BAP	Biotechnology Action Programme (of the EEC)
BPEO	Best practicable environmental option
BRIDGE	Biotechnology Research for Innovation, Development and Growth in Europe
CEC	Commission of the European Communities
DOE	Department of the Environment
DTI	Department of Trade and Industry
EC	European Community
EPA	(United States) Environmental Protection Agency
GEO	Genetically engineered organism
GMAG	Genetic Manipulation Advisory Group
HSC	Health and Safety Commission
HSE	Health and Safety Executive
IOV	(NERC) Institute of Virology
MAFF	Ministry of Agriculture, Fisheries and Food
NAS	(United States) National Academy of Sciences
NCC	Nature Conservancy Council
NERC	Natural Environmental Research Council
OECD	Organisation for Economic Co-operation and Development
OTA	United States Congress Office of Technology Assessment
TIBTECH	Trends in Biotechnology (Journal)
TREE	Trends in Ecology and Evolution (Journal)
UN	United Nations
UNEP	United Nations Environment Programme
UNIDO	United Nations Industrial Development Organisation
UPOV	International Union for the Protection of New Varieties of Plants
WHO	World Health Organisation

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