Fourteenth report : GENHAZ a system for the critical appraisal of proposals to release genetically modified organisms into the environment / chairman, Lord Lewis of Newnham.

ROYAL COMMISSION

ON

ENVIRONMENTAL POLLUTION

CHAIRMAN:
THE RT HON THE LORD LEWIS OF NEWNHAM

FOURTEENTH REPORT

GENHAZ

A SYSTEM FOR THE CRITICAL APPRAISAL OF PROPOSALS TO RELEASE GENETICALLY MODIFIED ORGANISMS INTO THE ENVIRONMENT

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JUNE 1991

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ROYAL COMMISSION
ON
ENVIRONMENTAL POLLUTION

FOURTEENTH 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.

'Yes, I have a pair of eyes,' replied Sam, 'and that's just it. If they wos a pair o' patent double million magnifyin' gas microscopes of hextra power, p'raps I might be able to see through a flight o' stairs and a deal door; but bein' only eyes, you see my wision's limited.'

Charles Dickens, *Pickwick Papers*

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CHAPTER 1

PURPOSE AND CONTENT

1.1 This Report describes an adaptation of the technique known as HAZOP to the search for potential hazards in the release to the environment of genetically modified organisms (GMOs)*. The Report includes a description of the resulting procedure — GENHAZ — that should facilitate its development through further trials using real proposals for release.

1.2 Our Thirteenth Report([3]) discussed both potential applications of GMOs and the uncertainties associated with their release to the environment. For reasons explained in that Report we took the view that the first consideration in the proper control of releases of GMOs was a thorough, expert scrutiny of every proposed release. We recognised the importance of a systematic and penetrating search for potential hazards. We drew attention to a procedure known as HAZOP (Hazard and Operability Study) that had proved very successful in identifying possible hazards, in particular in the chemical industry. HAZOP was devised as a technique to supplement traditional procedures for the design of safe manufacturing plant by a structured but imaginative examination of the design in operation.

1.3 During the preparation of our Thirteenth Report we met several scientists who were planning to release GMOs and we were impressed by the responsible manner in which they were exploring potential hazards. We felt that their task could be helped by the use of HAZOP-type techniques. It might seem strange that a procedure that had been developed to search for hazards in chemical manufacturing plant should be adaptable to living systems. However, unexpected interactions between seemingly safe components, or use under conditions that had not been envisaged, may lead to hazards as readily in ecosystems into which a GMO has been introduced as in complicated manufacturing plant.

1.4 The Commission therefore set up a small Working Party, with the collaboration of biologists and others from academic institutions, the Health and Safety Executive and ICI, to explore the feasibility of adapting HAZOP to the release of GMOs. The participants in the study (see Appendix 2) included people with experience in HAZOP studies, in genetic engineering, in ecology, in field trials and in general management.

1.5 The Working Party recognised that it would be difficult to apply HAZOP in all its detail to the release of GMOs but was able to devise a workable variant which incorporated the essential features of the HAZOP procedure. This was called GENHAZ. After development of GENHAZ using hypothetical releases, the procedure was tried out at the John Innes Institute, Norwich, in a two-day exercise on part of a real proposal for a release of a GMO. All who took part agreed that the procedure was very promising both in exposing potential hazards and as a planning tool. Lessons learnt in the trial have been incorporated in this report.

1.6 The Commission has now developed GENHAZ as far as it reasonably can. Further development needs to take place in the context of full trials of

* We use in this Report the term genetically modified organism (GMO) in place of genetically engineered organism (GEO) which we adopted for our Thirteenth Report. The former term has now become widely adopted and was used in the Environmental Protection Act 1990([1]) and in recent European Community Directives([2]). We use it in the same sense as we used GEO in our Thirteenth Report([3]).

GENHAZ on real proposals for release. This report is intended to provide sufficient material to undertake such trials and we recommend that the Government with the assistance of its Advisory Committee on Releases to the Environment (ACRE) should arrange for these to take place. The trials will, no doubt, suggest further modifications to the procedure. In the light of that experience and of advice from ACRE the Government should consider whether to integrate GENHAZ into the procedures for risk assessment of GMO releases and, if so, should prepare a users' manual drawing on this report and the outcome of the trials. In the light of the international interest in risk assessment of GMO releases, the Government should also take steps to encourage other countries to explore the use of GENHAZ.

1.7 We expect that experience with GENHAZ will lead to changes in detail and perhaps in structure that will make it even more appropriate to its task. We would encourage such developments provided that the comprehensive and systematic yet imaginative features of HAZOP are preserved. It will be desirable, should GENHAZ receive official acceptance, to develop an agreed standard procedure and then to make only agreed modifications.

1.8 The procedure set out in this report has been designed principally for experimental releases of plants and micro-organisms. We recommend that the Government should consider whether modifications might be necessary for application to proposals in areas such as genetically engineered vaccines and to proposals for releases of GMOs in commercial products.

1.9 A full GENHAZ study, like HAZOP, can require two to three weeks or more in aggregate (see paragraph 7.5). However, this is a small investment in comparison with the value of safe operation. Suggestions were made during the development of GENHAZ for simplifying the procedure in ways which might reduce the time required for a full study (see paragraph 7.11). The acceptability of such an approach can only be resolved through full trials. Experience with HAZOP has amply demonstrated, however, the value of devoting whatever time is necessary to a thorough search for potential hazards. We consider that a compressed procedure should not be adopted unless it has been proved in trials to be as effective as the full exercise.

1.10 It is to be expected that each laboratory will learn from its GENHAZ studies and, where appropriate, modify its practices to eliminate sources of risk which might occur in future projects. In addition, in the application of GENHAZ, general points will emerge that could sensibly be incorporated in advice on good practice for the design and implementation of release proposals. We recommend that the Government should review from time to time the outcome of GENHAZ studies to identify such general points and ensure that they are incorporated in appropriate advice documents. This would enable these points to receive attention independently of GENHAZ. As experience accumulates this should substantially reduce the time required for a GENHAZ study. However, very few releases will be exact replications of others. We therefore recommend application of GENHAZ to every proposal. Our recommendation is reinforced by experience in which seemingly innocuous modifications to operating chemical plant, previously subjected to HAZOP, have led to accidents. It is the practice in some organisations not to permit any modification of plant or range of operating conditions without reference to the previous HAZOP study, in order to ensure that the integral safety of the system will not be vitiated. Experience has shown that this practice has a further advantage in ensuring that proposed modifications receive more thorough scrutiny before they are implemented. This in turn leads to the modifications being more carefully thought through and reducing

the need for yet further modifications. Similar advantages can be expected from GENHAZ in leading to more carefully thought out proposals for release.

1.11 In order to perform their purpose of challenging the safety and operability of a project, both HAZOP and GENHAZ must be applied to detailed, definitive plans. However, in the trials of GENHAZ it became clear that additional application at an early stage in the planning of a release could generate perceptions that could significantly improve smooth running and the value of the results of a release experiment. GENHAZ is thus an effective tool for planning as well as for uncovering potential hazards. It draws attention to the importance of planning the genetic manipulation together with the release as a unified project.

1.12 It has been suggested that the name GENHAZ unduly stresses the hazard aspect over that of planning for good operation and may look like a warning notice. The name GENPLAN was suggested and was used in the addresses referred to below given to the British Association in Swansea and the University of Stirling. On reflection we prefer GENHAZ, the name in our Thirteenth Report, and have used it in this Report also.

1.13 We encouraged the presentation and publication of accounts of GENHAZ during the course of its development. Papers on GENHAZ were presented at an OECD workshop on safety in biotechnology in Paris in June 1989([4]) and (under the name GENPLAN) at the Annual Conference of the British Association for the Advancement of Science in Swansea in September 1990([5]). It was also described in the 1990 Robbins Lecture at the University of Stirling([6]).

1.14 The structure of the remainder of this Report is as follows. In Chapter 2 we explain the principles and procedures of HAZOP in the context for which it was designed, namely that of a chemical manufacturing plant. Examples from this context are, at this point in the presentation, likely to be more accessible to those familiar with HAZOP than examples from biological systems, which are given later in the report. Chapter 3 provides background to the science underlying the construction and release of GMOs for readers who have no previous acquaintance with it. In Chapter 4 we briefly sketch the work that led to the development of GENHAZ from HAZOP, draw attention to the very close relationship of the two systems and the reasons for the few differences, and indicate some aspects of GENHAZ that might repay refinement.

1.15 Chapters 5–7 are in effect a handbook for those who may wish to take GENHAZ further. Chapter 5 offers a condensed overview of GENHAZ, setting out the structure and introducing the terminology. Chapters 6 and 7 develop the procedure in detail, as it would be applied in practice. Chapter 6 describes the GENHAZ Questionnaire and its role in eliciting information about the release proposal. Chapter 7 explains the procedure for examination of that information by the GENHAZ study team. Chapter 8 outlines, by way of exemplification, part of the record of a GENHAZ study of a hypothetical release.

CHAPTER 2

HAZOP

2.1 This chapter provides a brief overview of the principles of HAZOP. Readers seeking a full authoritative account should consult texts such as those published by the Chemical Industries Association([7]) and the Institution of Chemical Engineers([8]). These documents have been very influential in developing GENHAZ and we are grateful to the publishers for permitting us to draw heavily on them for this report.

2.2 Safety in the design of industrial plant for chemical manufacture relies on the application of design codes which are based on the wide experience and knowledge of professionals in the industry. However, the scope of application of such codes is limited by the extent of the established experience and knowledge that underpins them. This may not, however, be adequate to identify and deal with all hazards that may arise from new technology, or even from known technology in new circumstances. It was the recognition of these limitations that led to the development of HAZOP as an additional step in the pursuit of safety.

2.3 It should be noted in passing that the perception expressed in the previous paragraph is especially important in the release of GMOs since, although many of the organisms that are currently being considered for release do not differ substantially from those that might arise naturally, this will not always be the case. The increasing power of genetic engineering is such that it is highly likely that organisms significantly different from those that might become established by natural means will be made and proposed for release, thus moving into territory in which there may be few guiding precedents.

2.4 In a HAZOP study, a multi-disciplinary team works on a design which has been drawn up in accordance with accepted good practice. The design will have taken into account such questions as:

- what chemicals flow through the various units of the plant?
- what reactions take place and at what rate?
- what should be the operating temperatures and pressures?

HAZOP is then used to look at the consequences of failure to control the operation of the plant within the intended limits, asking what would happen if something unintended were to occur despite the safety mechanisms and procedures already built in.

2.5 HAZOP takes as its starting point the line, flow and control diagrams that represent the *INTENTION* for the construction and operation of the proposed plant. Taking each item of the plant in turn, for example the pipe leading from a feed vessel to a reactor, HAZOP uses *GUIDE WORDS* such as MORE, LESS, OTHER THAN to focus attention on possible *DEVIATIONS* from what was planned, for example higher temperature, lower pressure, different chemicals. Each application of a guide word usually generates a number of potential deviations, for each of which possible *CAUSES* and *CONSEQUENCES* are worked out. *DEVIATIONS, CAUSES* and *CONSEQUENCES* are recorded along with the *GUIDE WORD*.

2.6 For example, a plant manufacturing a chlorinated hydrocarbon might have a pipe to convey chlorine into the vessel (the reactor) in which a reaction takes place with a hydrocarbon. Applying the guide word MORE to the flow of gas through the pipe would generate the deviation:

— more chlorine than intended flows into the reactor

This could have as a consequence the production of over-chlorinated product which, though commercially undesirable, might not of itself cause a hazard in the reactor. Even so, the possibility of generating hazards elsewhere in the plant must be considered. For example, another consequence of too much chlorine is likely to be the formation of more hydrochloric acid as a by-product than was planned. This could overload the scrubbers that were expected to absorb the acid, with the resultant possibility of hazardous release of acid to the atmosphere or corrosion of downstream equipment.

2.7 OTHER THAN would lead to consideration of a gas other than chlorine being fed to the reactor. Oxygen, for example, which might well be piped to the plant for some purposes, if fed to the reactor could cause an explosion. Of course all these obvious possibilities would almost certainly have been considered during the design. They are given by way of example. More recondite examples of the use of guide words are given later in the chapters that deal with GENHAZ.

2.8 Deviations and their causes, however seemingly improbable, are all recorded for evaluation. Indeed if the study, be it HAZOP or GENHAZ, fails to suggest some deviations that turn out to be totally improbable, then the team's imagination has not taken them far enough. Neither HAZOP nor GENHAZ provides a means of quantifying risks; both may need to be supplemented by other techniques when quantification is required.

2.9 If, taking into account the safety measures already envisaged, the deviation has a realistic cause and the probability of its happening is not so low as to be unrealistic, the team then investigates the potential consequences. If the deviation is judged to have both a realistic cause and hazardous consequences, then it will be necessary to consider what *ACTION* should be taken to deal with the hazard that has been exposed. Required action might be a measure to eliminate the hazard or a search for more or better information. If, on the other hand, no realistic cause of a deviation can be foreseen or if all the potential consequences are judged to be acceptable, then no action is necessary.

2.10 It is essential that the decision as to action, and the reasons for the decision, be clearly expressed in the record of the study, even when no action is necessary.

2.11 GENHAZ, like HAZOP, examines elements of the intention one by one but both procedures ensure that possible interactions across the proposal as a whole are explored.

2.12 No technique can guarantee that every hazardous possibility will be recognised, that the resultant risks will be accurately assessed or that the prescribed safety measures will be properly installed and maintained. Moreover, unremitting commitment by operators and management, encouraged by effective enforcement, is essential. All that can be claimed for HAZOP is that it has been successful in uncovering hazards that had not been recognised in the traditional course of design. In this respect it has received wide recognition. For example, Ozog and Bendixen assert([9]) that HAZOP is

the most versatile technique for hazard identification and that the most effective way to identify, quantify and control risks is to combine a hazard and operability study with fault tree analysis.

CHAPTER 3

A BRIEF INTRODUCTION TO GENETIC ENGINEERING

3.1 In this chapter we offer, in very simplified form, just enough information to enable readers who are not familiar with genetic engineering to follow the GENHAZ procedure and the hypothetical example in Chapter 8. A more detailed introduction is provided in Chapter 3 of our Thirteenth Report.

3.2 An organism's genes carry the instructions for the synthesis of biological catalysts, called enzymes, which in turn control the biochemical processes, including the synthesis of chemical compounds, that maintain life. Genes are made up of DNA which is a double helix composed of sequences of chemical units known as bases attached to chemical backbones (Figure 3.1). When a gene brings about the synthesis of the enzyme for which it conveys the instructions it is said to be expressed. The mechanism by which this occurs is complicated and need not be discussed here.

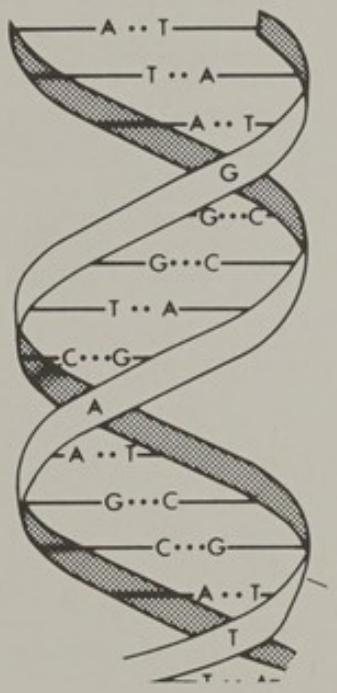

Figure 3.1 The DNA double helix showing the helical backbones joined by chemical units known as bases and identified as C, G, A and T.

3.3 If one or more of the bases is altered or deleted, the gene will be changed so that the instructions given to the various cells in the organism as to what chemicals to make and when and where, may be changed or may become meaningless. This is the basis of mutation and evolution as well as of genetically related diseases and is the cause of some cancers.

3.4 Organisms can sometimes follow the instructions encoded by a gene from another organism — as is the case in a viral infection. Thus if the gene coding for a compound normally produced by one species is introduced into

another, then the receiving organism may be induced to produce that compound, even though it is not a normal product of its metabolism. The introduced gene may be given a component, called a promoter, that determines its mode of expression to ensure, for example, its expression in the leaf of a plant and not elsewhere. The number of copies of a given gene present in a cell is known as its copy number.

3.5 Genes are transferred in nature from one organism to another by a variety of means. In the example used in Chapter 8 genes are introduced into a potato plant, through a wound on a leaf or tuber, by contact with a special bacterium containing a plasmid. Plasmids are loops of DNA that are not part of the bacterium's own chromosome but which may nevertheless be carried by and expressed in the bacterium (Figure 3.2).

3.6 Plasmids can be cut open by enzymes (of a type called restriction enzymes) and genes can be added to the resultant string of DNA (Figure 3.3). The plasmid loop can then be closed again. When a plasmid is to be used as a vector to carry a desired gene into an organism such as a plant an additional gene for resistance to an antibiotic, for example kanamycin, is often also inserted into the plasmid. After transfer of genes from bacteria to plant cells mixed populations of plant cells, some containing the plasmid, others not, are cultured in a growth medium containing kanamycin. Only those with the plasmid and gene conferring resistance to the antibiotic reproduce and form colonies. Plant cells containing plasmids that carry the desired gene can thus be separated from those that do not and used to regenerate whole plants in which all the cells contain the new genes.

3.7 The above explanation and the examples in this Report relate to the release of genetically modified plants. Techniques are available for genetically modifying an increasing range of living organisms and GENHAZ has been designed to be equally widely applicable.

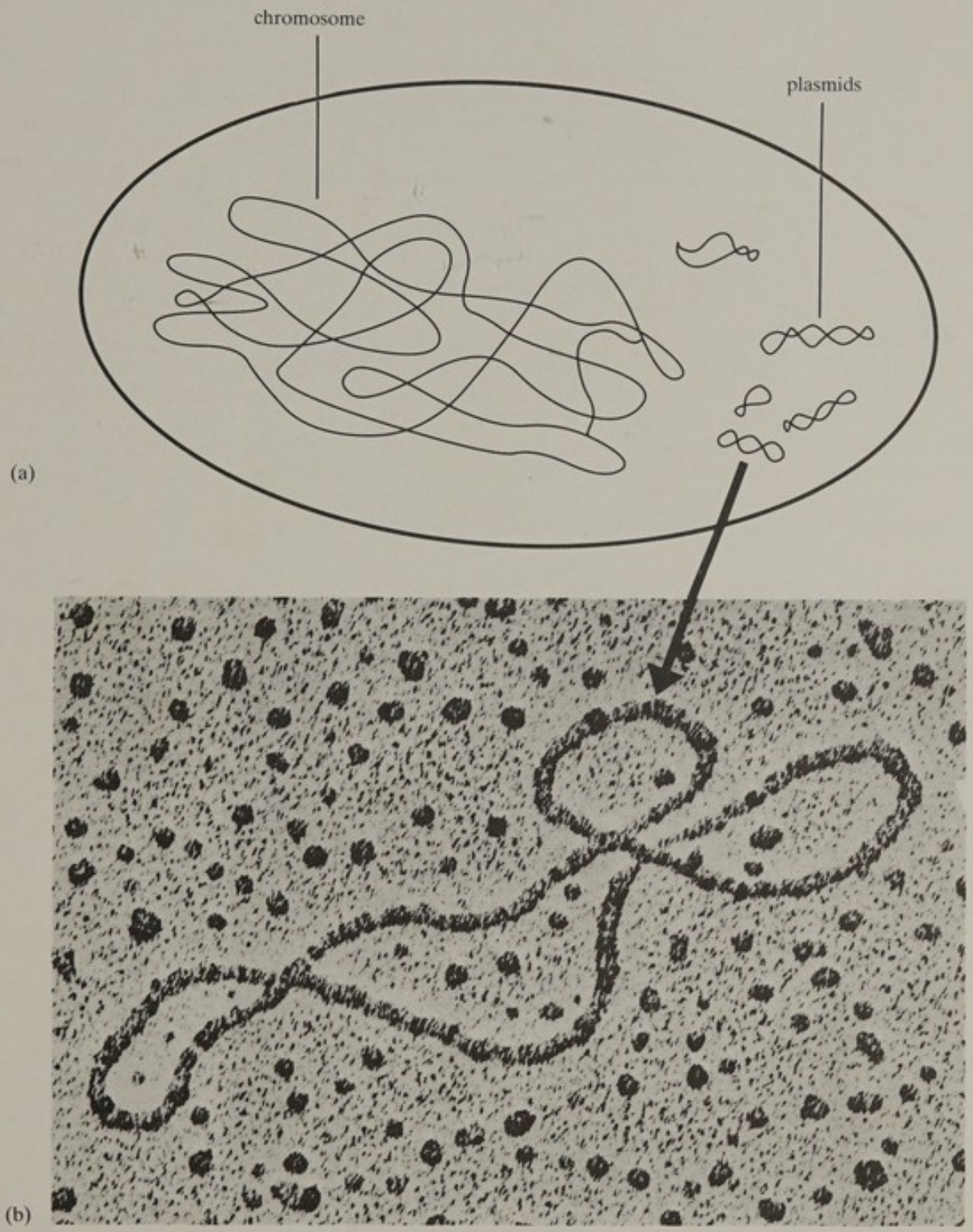

Figure 3.2 (a) A bacterium with chomosomal and plasmid DNA. (b) Plasmid photographed through an electron microscope.

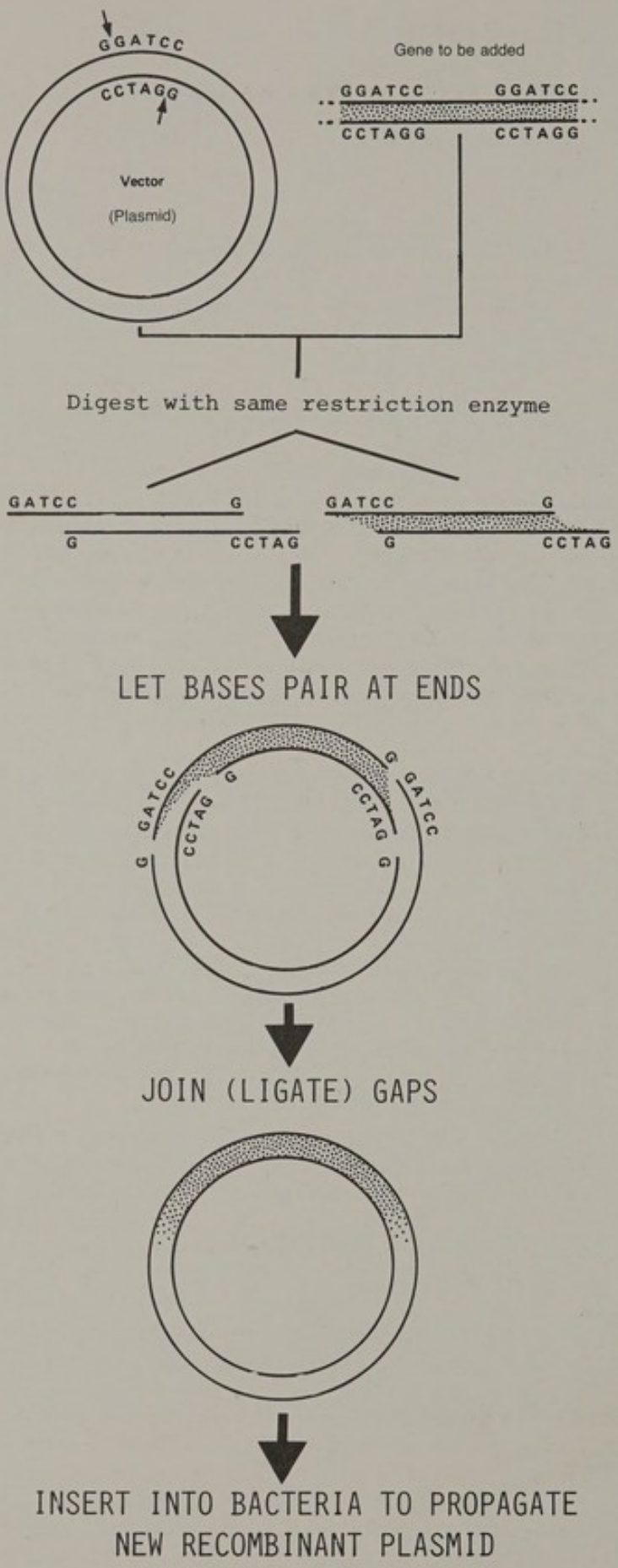

Figure 3.3 The use of a plasmid to introduce a gene into a bacterium.

CHAPTER 4

FROM HAZOP TO GENHAZ

4.1 In adapting HAZOP for the genetic engineering context the Working Party sought to stay as close as possible to the proven techniques of HAZOP and to make only such changes as were essential to encompass the special nature of living systems. With this in mind the first session was led by Dr Trevor Kletz, an authority on HAZOP.

4.2 As was explained in paragraph 2.5, the intended design and operation of a manufacturing plant is expressed in line, flow and control diagrams, which are used by the HAZOP team as the basic input to the study. It soon became apparent that the construction and release of a GMO could not conveniently be expressed in this way and that, even if it could, the information would be presented in a format that would not be consistent with patterns of thinking familiar to biologists. Moreover, although the impact of a chemical plant on its environment is an important consideration in a HAZOP study, the potential impact of the release of a living organism is far wider and less well understood and includes the possibility of mobility and replication of both organism and genes. These considerations add an extended environmental dimension that is not present in the case of a plant that manufactures a lifeless product.

4.3 The difficulty was overcome by an alternative means of expressing the design intention of a release experiment in a way which would enable it to encompass the behaviour and interactions of the living organisms concerned. The alternative approach for expressing the intentions, proposed by Dr Keith Powell, covered all stages of a project from the genetic modification, through the release to eventual clean up of the site and considered the impact of all the components of the genetically modified organism. This approach was subsequently augmented by answers to a questionnaire structured to correspond to the stages of the project and components of the GMO. The stages and components are defined in Chapter 5. The questionnaire, which was derived from the check list developed by the HSE's Advisory Committee on Genetic Modification, is explained in detail in Chapter 6.

4.4 The Working Party did not examine further the possibility of a diagrammatic representation of the intentions of a proposed release of a GMO. It is, however, possible that some form of diagrammatic representation of the various stages of a release might provide insights. Diagrammatic representations of genetic engineering processes themselves are, of course, standard practice.

4.5 It was found expedient to change slightly the HAZOP set of guide words to take account of possibilities peculiar to biological systems.

4.6 In HAZOP, *causes* of *deviations* are considered (see, for example, paragraph 2.5 above and page 2 of the Chemical Industries Association's Guide to HAZOP([7])). In GENHAZ, however, we relate *causes* to *consequences* because, in the natural environment, there will often be causal links between deviations and consequences and along chains of consequences. Moreover, we wish to focus attention onto the identification and evaluation of potential consequences, since it is the nature and impact of these that will largely determine the future of GMO releases.

4.7 In HAZOP each deviation is considered in order to decide how it could be caused and what would be the consequences. In GENHAZ we suggest that, for each deviation, the team first generates possible consequences and then assesses them to decide which are unacceptable. Realistic causes are then sought for unacceptable consequences. Of course, if no realistic cause can be adduced for a deviation, then no consequence that follows from that deviation alone will have a realistic cause. Consequences that are judged to be potentially hazardous and to have a conceivable cause are noted for remedial action. The outcome is essentially the same as it would have been under the HAZOP protocol but the emphasis on the various steps is slightly different.

4.8 A GENHAZ examination of a questionnaire could last two to three weeks, working a half day only as is recommended for HAZOP. Further time would be needed for a re-examination if additional information were required or if the first examination led to changes in the design intention that could not be taken into account at the time. However, the objection that a GENHAZ exercise is too time consuming does not carry weight — at least until something equally effective and less demanding of time is found. The importance of identifying all serious hazards, not to mention the saving in getting things right first time, will far outweigh the time spent on the exercise.

4.9 As an aside and unrelated to hazard, we would suggest to scientists who may find the HAZOP/GENHAZ procedure congenial that a similar approach could be used to help to envisage new possibilities for experimental designs which had hitherto been unconsidered and for selection of research strategies. The application of guide words encourages lateral thinking and forces attention onto possibilities that might not have been considered, or might have been rejected out of hand without adequate consideration.

4.10 In summary GENHAZ, based on HAZOP, has the following attributes:

(a) it is a review by a multi-disciplinary team of the behaviour of individual elements of a planned release in the context of the whole system in operation;

(b) it forces an exploration of the hazards that might arise, however improbably, if the process were to operate in ways that were not intended;

(c) it leads to an evaluation of the resultant risks, by appropriate techniques, and to action that should be taken to counteract unacceptable risks that arise from hazards that are judged to be realistic;

(d) it is effective at an early stage as a planning tool, as well as in exposing potential hazards in the ultimate proposal for release.

4.11 After GENHAZ had been worked out and tested, with encouraging results, on parts of hypothetical studies it was applied in a two-day exercise to part of a real proposal for a release of a GMO at the John Innes Institute in Norwich, by kind invitation of the Director, Professor Richard Flavell. The Director and members of his staff were joined in the exercise by scientists from the HSE, ICI and the Royal Commission. Again the outcome was very encouraging and the trial demonstrated the viability of the approach. The handbook prepared for participants was modified and restructured to take account of lessons learned and is incorporated in Chapters 5–7 of this report.

4.12 The exercise at the John Innes Institute demonstrated very clearly the potential value of GENHAZ as a planning tool if applied early in a project

(paragraph 1.11). This is not surprising since the more carefully the consequences of a proposed action are examined the more likely it is that all relevant factors will be recognised, with advantages for experimental design, project development and effective operation as well as in the reduction of risk.

4.13 Drawing up a questionnaire that would generate statements of intent to which guide words could be effectively applied was a principal task in developing GENHAZ. As will become clear after reading the following two chapters, the current set of questions could probably be improved, drawing on experience with their use, in respect of coverage of the plan and aptness for the application of guide words. It may well be that the set would need to be modified for some releases.

CHAPTER 5

THE GENHAZ PROCEDURE IN OUTLINE

Introduction

5.1 This chapter sets out the formal structure, the framework, of GENHAZ and introduces the terminology. Both structure and terminology are explained in more detail and exemplified in Chapters 6 and 7.

5.2 The GENHAZ framework has four main elements:

i. a series of questions about the release — the GENHAZ questionnaire — the answers to which provide a statement of intent for examination by the GENHAZ study team;

ii. two elements used to structure and to focus the use of the questionnaire:

— the components of the genetically modified system itself; and

— a set of seven stages describing the construction and release of a genetically modified organism;

iii. the procedure for following a GENHAZ study;

iv. a set of guide words which provide the essential aids to the interrogation by the team of the design intention of the release proposal.

These elements are shown in Figure 5.2 opposite. Figure 5.1 defines the terms, borrowed from HAZOP, used to describe the GENHAZ procedure.

INTENTION	What is intended to happen during, or as a result of, the release.
DEVIATION	a departure from the intention uncovered by systematically applying the guide words.
CONSEQUENCE	a result of a deviation.
CAUSE	means by which a consequence could occur.
ACTION	a step to be taken as a result of identifying a serious consequence with a realistic cause.

Figure 5.1 Terms used in the GENHAZ procedure (based on HAZOP)

5.3 It will be helpful to summarise the structural elements of the questionnaire before introducing the questionnaire itself.

The genetically modified system

5.4 An essential part of the GENHAZ analysis is of course a consideration of the construction and behaviour of the genetically modified system which is the subject of the release. It is helpful to distinguish three COMPONENTS of that system. For illustrative purposes, the following description of a genetically modified system assumes an experiment using recombinant DNA (rDNA) techniques in which DNA is introduced into the host organism by a

Design Intention	GENHAZ Questionnaire's answers		
Components of the genetically modified system	CONSTRUCT	RECIPIENT	PRODUCT
Stages of the release	MAKE or SELECT RELEASE ESTABLISH POPULATION GENETIC TRANSFER MONITOR TERMINATION/CLEAN UP		
GENHAZ Procedure	INTENTION DEVIATION CONSEQUENCE CAUSE ACTION		
Guide words	NO/NOT AS WELL AS WHERE ELSE	MORE PART OF	LESS OTHER THAN WHEN ELSE

Figure 5.2 The main elements of the GENHAZ framework.

vector system. The GENHAZ approach is, however, of general applicability and could be modified for other forms of genetic engineering. For the purposes of GENHAZ three components of a genetically modified system in an rDNA experiment are distinguished:

i. the CONSTRUCT made up, for example, of nucleic acid from a gene donor and of a vector (eg a plasmid) which enables the gene to be replicated, bulked up and hence transferred to the new host;

ii. the RECIPIENT or HOST into which the construct is transferred; and

iii. the PRODUCT, which is the genetically modified organism itself, and might be regarded as the sum of the CONSTRUCT and the RECIPIENT. It is nevertheless convenient, if formally inaccurate, to describe it as a component.

5.5 The application of the guide words (paragraph 5.10) to construct and recipient, as well as to product, at all stages of the release recognises the fact that consideration of the interactions of the construct and the recipient with the environment may generate thoughts as to those of the product. Moreover, the construct and recipient may themselves occur separately in the environment as a result of the release.

The seven stages of a release

5.6 Seven stages in the release process are defined in GENHAZ. The first of these, MAKE or SELECT, is relevant independently to each of the three components of the genetically modified system. The remaining six are relevant to the system as a whole but the team will nevertheless consider the behaviour or influence of each component at each stage. Thus RELEASE is concerned with the release of the product but questions in section 2.1 of the questionnaire are specifically about the effect of the recipient during the release of the product, not about the release of the unmodified recipient. In practice, consideration of the potential effects of all three components can sensibly be discussed together when considering the last six stages.

5.7 The seven stages are:

i. MAKE or SELECT – the selection of the recipient, the preparation of the construct and its incorporation in the recipient to form the product.

ii. RELEASE – the process of introducing the product into the release environment.

iii. ESTABLISH – the events during the period following the release during which the product either settles in and establishes itself in the release environment, or fails to do so. This stage overlaps with the next and it may prove convenient to discuss them together.

iv. POPULATION – the pattern of growth, spread and reproduction that follows the initial period of establishment; the interaction of the product and the release environment.

v. GENETIC TRANSFER – the unintended transfer of DNA from any component into other DNA, at any stage of the release.

vi. MONITOR – the monitoring of the progress and outcome of the release.

vii. TERMINATE AND CLEAN UP – what is planned either for when the trial has been completed or in the event of an early termination proving necessary.

The GENHAZ questionnaire

5.8 The answers to the GENHAZ questionnaire describe how the genetically modified system is to be created, the manner in which the release is to be carried out and the possible environmental impacts. In other words they set out the plan and its context. We refer to the answers as statements of intent or 'statements' for short. They take the place of the various diagrams which define the design and express the operating intentions in HAZOP.

5.9 The questions are laid out in seven sections corresponding to the stages of the release. Within each section groups of questions relate to each of the components of the genetically modified system. The questionnaire is given in full on pages 22–27. Examples of how it can be used constructively and explanations of some questions and the intentions behind them are given in the commentary in paragraphs 6.6–6.17 and in paragraph 7.14.

Guide words

5.10 The GENHAZ guide words force the team to consider deviations from the intentions. As each stage of the release is considered, the guide words are applied one by one to answers to the questionnaire to suggest ways in which outcomes may depart from the plan. More than one deviation could be generated by any one guide word and the same deviation might arise from more than one combination of guide word and statement of intent. Not all guide words will necessarily be meaningfully applicable to all statements. The complete list of guide words is given in Figure 5.3 opposite.

5.11 Using the structure, concepts and terminology that have been described, a GENHAZ study follows the steps set out opposite in Figure 5.4. This procedure is explained in detail in Chapters 6 and 7.

NO or NOT	a complete negation of the. intention (eg a gene fails to insert into a vector)
MORE	a quantitative increase (eg the level of expression of a gene is greater than had been expected); could also be applied to time in terms of duration or frequency
LESS	a quantitative decrease (eg the deflowering of plants to prevent spread of pollen is incomplete); could also be applied to time in terms of duration or frequency
AS WELL AS	a qualitative increase — something additional to the design intention happens (eg insects other than those targeted by a gene product are killed)
PART OF	a qualitative decrease — something less than the design intention happens (eg one of the genes inserted into the recipient fails to express)
OTHER THAN	something quite different from the design intention happens (eg the wrong construct is inserted)
WHERE ELSE	an intended event takes place in a location other than that planned (eg genetic material or the product of its expression occurs elsewhere than was planned)
WHEN ELSE	some effect appears at a time different from that expected (eg a modified plant flowers earlier or later than its unmodified form even though this was not the purpose of modification).

Figure 5.3 Guide words and their meanings

Before the study team meets:
Answer the questions in the questionnaire

At the study team meetings:
Step 1 Apply the GUIDE WORDS to the answers and generate *DEVIATIONS*
Step 2 Develop possible *CONSEQUENCES* of each *DEVIATION*
Step 3 Examine each *CONSEQUENCE*, decide whether it is sufficiently serious to require *ACTION* to be taken to avoid it and, if so, whether it has a realistic *CAUSE*
Step 4 Decide what *ACTION* should be taken

After the meetings:
Step 5 Implementation and reference back to the GENHAZ team

Throughout:
Maintain an audit trail.

Figure 5.4 The steps in a GENHAZ study

CHAPTER 6

ANSWERING THE QUESTIONNAIRE

Introduction

6.1 This chapter describes in some detail the provision, in the form of answers to the questionnaire, of a statement of what is intended when the proposed release takes place. The questionnaire itself is set out in full at the end of this chapter on pages 22–27.

Answering the questionnaire

6.2 The answers to the questionnaire, the statements of intent, will provide a description of the release proposal, setting out the intentions in sections dealing with the seven stages of the release and the three components of the genetically modified system. The answers will describe what is to be done in preparation for the release and during the release itself, what is expected to happen as a result and the factors that are likely to affect what happens.

6.3 Since the answers to the questionnaire provide detailed statements of the intentions of the proposal, this part of the process should be completed by the release team before the start of the formal GENHAZ exercise but when the design of the release is complete. Any changes made in the design after the questionnaire is answered will compromise the GENHAZ exercise, which must be carried out on the final design. If changes to the intended procedure are made subsequent to the completion of the GENHAZ study, then all statements of intent that are changed must be re-examined by the GENHAZ procedure.

6.4 However, experience has shown that it can also be very useful to the release team to answer the questionnaire and carry out an initial GENHAZ study before the design of the experiment is finalised, as suggested in paragraph 1.11. Answering the questions forces attention on to any areas of ignorance and uncertainty in the proposals thereby bringing into sharper focus perceptions of both the objective and the means of achieving it. This can lead to improvements in the design of the experiment before it is finalised, at which time the questionnaire can be answered again in preparation for the main GENHAZ study. As experience of GENHAZ progresses, a checklist including considerations raised in previous studies could be employed at the planning stage. Early application of GENHAZ, though valuable for planning, is not a substitute for the use of GENHAZ to provide the essential testing of the final design, when it will give the maximum protection against overlooking potential hazards.

A commentary on the questionnaire

6.5 GENHAZ has been designed to apply to the release of any genetically modified organism. This should be borne in mind in reading the questionnaire for the first time. It will be apparent, for example, that some questions are more appropriate to the release of, say, a micro-organism than to a vascular plant and *vice versa*. The remaining paragraphs of this chapter offer some comments on the thinking behind the questionnaire to help the reader understand the approach to GENHAZ that will be most productive.

Searching questions

6.6 The questionnaire is divided into seven sections corresponding to the seven stages of the release process. Each section is in turn divided into three,

reflecting the components of the genetically modified system. Some of this may seem to lead to repetitive consideration of the same points under different questions, but setting the questions in such specific contexts should help to focus the line of thought and to encourage in-depth consideration of each issue. In preparing the questionnaire the intention has been to make each question as searching as possible, rather than allow easy assumptions to be made.

6.7 Thus question 1.1.3, **'What is the pathogenicity of the recipient organism to man, animals, plants and micro-organisms?'** should encourage the respondent to think of all possible pathogenic effects, whereas a question, **'Is the organism pathogenic?'** might have allowed the respondent to overlook the possible effects on an organism that was not a target for the release. An example arose during a trial of GENHAZ on a hypothetical experiment to release a plant modified to be resistant to an insect pest. The possibility was raised of pollen in which a foreign protein was expressed causing an allergic reaction in people.

6.8 Another example is question 1.2.6, **'What instability of the construct is known or might occur?'** This should encourage the respondent to think of circumstances that might give rise to instability so that a claim that there was no instability would be based on strong grounds. The alternative question, **'Is there instability?'** might produce the answer, 'No,' which could be accepted easily, closing the door on deeper thought.

6.9 The intention of searching out full responses to the questionnaire does not preclude an answer 'None' or 'Not Applicable'. Question 1.1.2, **'What is the host range of the recipient organism?'** was devised with micro-organisms in mind. If the plan is for the release of, say, a modified vascular plant, the answer might be 'None'. Even then, the guide words should be applied to generate deviations. Thus applying MORE could lead to discussion of the plant becoming, say, a parasite as a result of the genetic modification. The possible consequences of this could then be considered. However, in some cases the GENHAZ team may legitimately decide that these deviations or consequences have no realistic cause and therefore merit no further detailed consideration.

Accurate responses

6.10 It is important that each question in the questionnaire is fully and accurately answered. It may sometimes not be possible, however, to answer a question adequately, especially when it is attempted early in the planning. If lack of knowledge means that an answer cannot be comprehensive, stating, 'We do not know,' recognises the need for further information and allows the team to progress. The recognition of uncertainty and ignorance is, of itself, valuable. It is then necessary to consider the consequences and realism of a range of possibilities, including the most unfavourable.

6.11 An example is provided by question 1.3.1, which is used for the hypothetical study described in Chapter 8, **'By what means will the construct be inserted into the recipient, and how much of it will be inserted, to make the product?'** If the answer to 'how much' is unknown, as in the example on page 37, the team must consider a range from none to the maximum conceivable and decide whether the full range is acceptable.

Setting boundaries

6.12 Some of the questions are deliberately open ended. Thus 2.1.3, **'What undesirable effect might the recipient have on the release environment?'** could take the GENHAZ team a long way down a series of chain reactions. The

team, under the guidance of the team leader, must take decisions as they go through the study about how far some issues should be explored. It is not possible or necessary that GENHAZ should predict the whole sequence of events including the consequences. The function of the study is to ensure that possible adverse consequences are recognised as far as possible, even if full consideration is deferred to a later or quite different study (see also paragraph 7.13).

Donor, vector and construct

6.13 Information is sometimes sought on the donor and vector used to form the construct. These aspects have been incorporated within section 1.2 of the questionnaire. For example, question 1.2.2, **'What is the source of the nucleic acid to be modified?'** seeks identification of the donor. Application of the guide words will lead to discussion of the possibilities of transferring none, part of, more of or even the wrong part of the donor's nucleic acid to the construct, and therefore to the recipient. Instability in the donor might be considered under MORE THAN, LESS THAN or OTHER THAN. OTHER THAN also raises issues such as the possibility of the same or similar genetic sequences or different sequences being inserted, by accident or design. A useful strategy, when in doubt as to whether something might conceivably happen, is to try to envisage a research programme that might uncover a way of making it happen. Trying to make an event happen, at least mentally, is a good way of testing its feasibility. Consequent action that the team might consider recommending is that donor nucleic acid be checked for purity and correctness at the time of insertion, especially if it is derived from a DNA collection.

6.14 Three questions, 1.2.3 **'What modifications will be made to this nucleic acid?'** 1.2.4, **'What is the intended purpose of each modification?'** and 1.2.5, **'What will be the structure of the finished construct?'** should evoke, *inter alia*, answers about the excision of the required nucleic acid, the use of vectors to transfer it and the structure of the construct after modification is complete. The guide words will generate an array of possible deviations from the planned operations. Question 1.2.4, on the purpose of each modification, refers to the engineering of the construct. Thus one modification might be to isolate a specific functional gene and a marker gene, while another might be the insertion of it into a plasmid vector. The question of the purpose of the construct is dealt with under 1.2.1, **'What is the intended function of the finished construct?'**

Unexpected perceptions

6.15 Generating responses that are unexpected is central to GENHAZ. Question 4.2.2, **'What limitations has the construct on its ability to survive?'** assumes that the construct can survive, stimulating a wider exploration of possibilities than a question such as, **'Will the construct survive in the environment after the experimental period?'** which might merely generate a less informative yes or no answer.

6.16 Another example of the GENHAZ team's being encouraged to look from an unexpected angle is question 4.3.4, **'How would the product population be affected by extremes of climate — eg flood, drought, high and low temperatures?'** The environment tends to be thought of as stable but in practice large natural variations can occur even in apparently stable environments. A question as to whether the ecology of the release site could change over the period of the trial, for reasons not connected with the released organism, does not appear in the questionnaire. It may be desirable to insert such a question as circumstances in which such a change could take place

could be envisaged — for example the descent of a locust swarm, or the germination of seeds of plants not normally present, as a result of burning over or deep cultivation in preparation for planting out.

6.17 This commentary on the questionnaire is not intended to provide an answer to every question that might arise in the course of a study, still less to constrain the range of thought. Rather it is intended to serve as a guide, an indication of the approach that should be adopted by the GENHAZ team if it is to complete the exercise in a way that both searches out the possible hazards of the proposed release and satisfies the team itself. This approach is one that will also ensure the effective achievement of the release purpose.

The questionnaire

6.18 The GENHAZ questionnaire is laid out by STAGE; each stage then being sub-divided into sections relating to each COMPONENT. Except in stage one, MAKE or SELECT, where each component should be considered separately, each STAGE relates to the whole genetically modified system and the questions in each sub-section relate to the influence of the particular COMPONENT at the stage in question.

6.19 The answers to this questionnaire, which we have called statements of intent or 'statements' for short, would normally be accompanied by a narrative description of the release proposal and form the principal data source for the GENHAZ study. Although, in the course of the GENHAZ discussions, it may be appropriate to consider groups of questions and answers together when applying the guide words, as discussed in paragraph 7.10, it is important that each question should be considered separately when completing the questionnaire for, by being quite specific, they provide a check that all aspects of the release are considered.

STAGE 1 MAKE or SELECT

1.1 RECIPIENT

1.1.1 What is the recipient organism? How will it be identified? What checks will be made that the organism used is actually the intended recipient?

1.1.2 What is the host range of the recipient organism?

1.1.3 What is the pathogenicity of the recipient organism to man, animals, plants and micro-organisms?

1.1.4 To what extent is the recipient already a genetically modified organism?

1.2 CONSTRUCT

1.2.1 What is the intended function of the finished construct?

1.2.2 What is the source of the nucleic acid to be modified?

1.2.3 What modifications will be made to this nucleic acid?

1.2.4 What is the intended purpose of each modification?

1.2.5 What will be the structure of the finished construct?

1.2.6 What instability of the construct is known or might occur?

1.3 PRODUCT

1.3.1 By what means will the construct be inserted into the recipient, and how much of it will be inserted, to make the product?

1.3.2 What is the intended function of the finished product?

1.3.3 What is the expected copy number of the finished product and what will control it?

1.3.4 What is the intended level of expression of the introduced gene(s) in the product?

STAGE 2 RELEASE

2.1 RECIPIENT

2.1.1 What desirable effect does the recipient have on its native habitats?

2.1.2 What undesirable effects is the recipient known to have on any habitat?

2.1.3 What undesirable effect might the recipient have on the release environment?

2.2 CONSTRUCT

2.2.1 In what hosts might the construct cause concern?

2.2.2 What change in the pathogenicity of the recipient, to any organism, might occur as a result of the introduction of the construct?

2.2.3 What undesirable effects might occur as a result of a change in the construct?

2.3 PRODUCT

2.3.1 What will be the method of release and the dose, timing and frequency of application?

2.3.2 What physical containment of the product, and of any viable parts of it, will be put in place?

2.3.3 What is the target and what are the predicted effects of the product on it?

2.3.4 What are the predicted effects of the product on non-target habitats eg related species?

2.3.5 What are the predicted effects on non-target organisms?

STAGE 3 ESTABLISH

3.1 RECIPIENT

3.1.1 What factors affect the likelihood of the recipient establishing in the release environment?

3.2 CONSTRUCT

3.2.1 How might environmental and ecological pressures affect the construct within the product?

3.3 PRODUCT

3.3.1 What internal and environmental factors affect the likelihood of the product establishing in the release environment?

3.3.2 What limitations on the establishment of other organisms might be caused if the product became established, thereby pre-empting an ecological niche?

STAGE 4 POPULATION

4.1 RECIPIENT

4.1.1 What factors affect the increase, decrease and dispersal of the recipient in:

(a) its habitats; and

(b) the release environment?

4.1.2 What long term survival or dispersal forms can the recipient adopt?

4.1.3 To what extent will changes in the recipient population influence other species:

(a) in the same trophic level; and

(b) in other trophic levels?

4.2 CONSTRUCT

4.2.1 What factors, internal and external, affect the increase, decrease or dispersal of the construct?

4.2.2 What limitations has the construct on its ability to survive?

4.3 PRODUCT

4.3.1 What factors affect the increase, decrease and dispersal of the product in:

(a) its habitats; and

(b) the release environment?

4.3.2 What intrinsic limitations to its survival does the product have?

4.3.3 How could the product grow and/or multiply in non-target habitats?

4.3.4 How would the product population be affected by extremes of climate — eg flood, drought, high and low temperatures?

STAGE 5 GENETIC TRANSFER

5.1 RECIPIENT

5.1.1 What genetic instability is known or might occur in the recipient?

5.1.2 What transfer of genetic material from the recipient to another organism might occur?

5.2 CONSTRUCT

5.2.1 By what means is the genetic construct known to be transmissible?

5.2.2 What other transmission mechanisms might operate?

5.3 PRODUCT

5.3.1 What genetic instability is known or might occur in the product?

5.3.2 By what means might genetic material (eg DNA) be transferred from the product to other organisms?

STAGE 6 MONITOR

6.1 RECIPIENT

6.1.1 How, where and when will the presence of the unmodified recipient be monitored?

6.2 CONSTRUCT

6.2.1 What factors in the construct allow monitoring of its nucleic acid?

6.2.2 What uncertainties are there as to the structure of the construct?

6.3 PRODUCT

6.3.1 What uncertainties are there as to the genetic structure of the product?

6.3.2 What will be monitored; when, where, how and at what level?

6.3.3 How will the product be distinguished from the wild type recipient?

STAGE 7 TERMINATE AND CLEAN UP

7.1 RECIPIENT

7.1.1 What measures will be taken with the recipient if termination and/or clean up is necessary?

7.2 CONSTRUCT

7.2.1 What measures will be taken with the construct if termination and/or clean up is necessary?

7.3 PRODUCT

7.3.1 What events would trigger the termination of the experiment?

7.3.2 How would termination and clean up be effected?

7.3.3 What could frustrate the effectiveness of the chosen procedures to terminate and clean up?

7.3.4 What viable product would remain after clean up?

CHAPTER 7

THE GENHAZ STUDY TEAM AT WORK

The study team

7.1 A GENHAZ study is undertaken by a team of people working together, rather than by individual specialists examining aspects of the design in isolation. Such teamwork increases the likelihood of lateral thinking when applying the guide words. A team with a wide range of expertise is necessary.

7.2 The GENHAZ study team should include scientists from all relevant disciplines so that, among others, genetics, ecology, and safety are represented, the last mentioned by a representative of the laboratory biological safety committee. The composition of the team should not necessarily be restricted to the disciplines involved in the release project. While it will be necessary, in the case of a genetically modified plant, to have strong representation from plant sciences, other specialists such as zoologists may well bring valuable insight on the possible effects of the modified plant on animals. It is important that expertise in field trials is included in the team as well as laboratory researchers.

7.3 The team should be drawn mainly from those who have planned and from those who will carry out the release, since it is on them that the responsibility for safety and efficacy rests. Like HAZOP, GENHAZ provides an environment in which those who have designed a process can take a fresh and uninhibited look at it. Some people who are not directly involved in the release should also join the team. There is no need for all the members of a GENHAZ team to be asociated with the organisation proposing the release. Outside experts can be brought in if desired. This may be particularly important for small organisations without recourse in-house to the full range of expertise.

The team leader

7.4 A GENHAZ study requires a team leader who is familiar with the operation of GENHAZ and who will thus be able to guide the rest of the team through the matrix of questionnaire and guide words systematically and efficiently. The guide to HAZOP published by the Chemical Industries Association([7]) distils much valuable experience of HAZOP studies which is highly relevant to GENHAZ also and likely to be extremely useful to GENHAZ team leaders. The leader does not need to be a specialist in the subject of the release, indeed it may be easier to avoid blind spots induced by familiarity if he is not, but he or she should have sufficient technical knowledge to be able to understand and control the discussions.

7.5 The leader should estimate the expected duration of the GENHAZ study and arrange that team members and facilities are available. Practitioners of HAZOP have found that the best progress is made if study meetings are restricted to mornings only and to only two or three sessions in a week. However this may not be practicable for every study. An important task for the team leader is to maintain the enthusiasm and the imaginative and positive approach of the team to the exercise which, though often exhilarating, can also be very demanding.

Training

7.6 While it would be helpful if the whole GENHAZ study team were experienced in the procedure, and indeed this may come about in the long

term, the team leader and those team members keeping the record, as a minimum, should undergo some training prior to the start. It would be beneficial if a third person, who would play the role of prompter, checking that each and every section of the questionnaire and procedure had been addressed in the course of the study, could also receive some training. If our recommendation in paragraph 1.6 is accepted and GENHAZ becomes part of the procedures for risk assessment, then we recommend that the Government, with the advice of its Advisory Committee on Releases to the Environment, should develop a training programme for GENHAZ team leaders and other participants.

Preparing for the study

7.7 Some preparatory work is required before the study can begin so that the exercise can be carried out efficiently and effectively. The release team must provide the initial responses to the questionnaire and it may be appropriate for additional explanatory material about the release proposal to be provided. As the study proceeds there may be a call for further information. The leader must have a plan for the progress of the study and he must arrange the necessary meetings of the study team.

Recording the GENHAZ study

7.8 The working record can be kept, during the course of the study, in a tabular form with headings for the component, stage and guide word, and columns in which the team note down the deviations, consequences and causes identified together with the train of thought that leads to the proposed actions. Alternatively or additionally the record could be kept in sequential form. The tabular form is likely to be most convenient for noting on a flip chart as the exercise progresses, while a designated recorder might keep a fuller record of the discussion in sequential form. Examples of these two formats are provided in Figures 7.1 and 7.2 overleaf. The working record, in whatever form, may need to be tidied up, but not altered in content, for others to study. The originals should be kept. The record will allow the study to be reviewed if for any reason this is desirable; for instance, if the procedures are modified, or in the event of unexpected consequences.

Study team meetings

Step 1: Apply the guide words to the answers and generate deviations

7.9 The study team begins its work by applying the guide words to activities or events that are specified or implicit in the statements of intent described in the responses to the questionnaire. It will probably be found convenient to divide the step into elements formed by combinations of stages and components, thus:

MAKE/SELECT and RECIPIENT
MAKE/SELECT and CONSTRUCT
MAKE/SELECT and PRODUCT
RELEASE and PRODUCT etc

7.10 Applying the guide words in turn will suggest deviations from the intentions. In practice, it may prove effective to consider groups of questions and answers together. This will particularly be the case for those questions which ask for information about the likely consequences of the release and about the factors which may affect the consequences. These questions can conveniently be taken together with related questions asking for information about the intentions of the release proposal. Answers to questions about intentions will provide material for the application of guide words while answers to questions in the other categories will serve to spark ideas in the

Stage: Component: Guide word:

Deviation	Consequences	Causes	Actions

Figure 7.1 Tabular format for recording GENHAZ study.

Title of study: Date:

Stage: Component:

Question:

Answer:

Guide word:

Deviation:

Consequences

Causes:

Actions:

Figure 7.2 Sequential format for recording GENHAZ study

minds of team members when considering possible consequences of deviations. Thus all the statements resulting from, say, section 6.3 of the questionnaire (Monitor — Product) might be considered together since the answers to 6.3.2 and 6.3.3 describe the monitoring intentions while 6.3.1 is a factor relevant to consequences of deviations from intention. Indeed in some cases it may be possible to take an even larger group at one time, so that the whole of section 6 is considered at once. In paragraph 5.7 we noted that in some studies two stages — Establish and Population — could perhaps be considered together. If and when several groups or sections are taken together the team must take great care not to omit consideration of any section through its being considered together with others.

7.11 A suggestion was made during the development of GENHAZ that the elements described in paragraph 7.9 above, constructed from combinations of stages and components, should always form the basis for the GENHAZ study. The answers to all questions relating to each element would, in this approach, always be considered together and would provide ideas both for the application of guide words and the generation of consequences. It was suggested that this might reduce the time needed to carry out a GENHAZ study, offer more scope for open-ended consideration of deviations and consequences, and reduce the risk of confusion when guide words are applied to answers to overlapping questions.

7.12 We would emphasise that the above suggestions derive from a very limited experience of GENHAZ. No final conclusion was reached on the extent to which answers to questions might usefully be combined when applying guide words or on the risk that this might reduce the probability of recognising all possible hazards. These are matters that can only be resolved by experience but it is essential that no procedure should be adopted which enables a challenge to any of the intentions to be by-passed. Experience with HAZOP has amply demonstrated the value of devoting whatever time is necessary to a thorough search for potential hazards.

Step 2: Develop possible consequences of each deviation

7.13 The GENHAZ team must consider carefully the implications of the deviations generated by applying the guide words. This is the second point where imagination is essential in using GENHAZ to uncover the possible consequences of the release not going according to plan. Given the very long chains of events associated with some ecological consequences and the time scale over which they may take place the team must decide how far it is reasonable to go. It may sometimes be the case that the initial consequences of a deviation will be relatively unimportant but that more serious impacts will arise in the longer term. For possible review by others, the point at which analysis of the chain of consequences is ended must be recorded together with the reasons (see paragraph 7.18).

7.14 GENHAZ will encourage thought about consequences even where immediate answers or the application of guide words may seem to suggest there is nothing to consider. Question 6.1.1, **'How, where and when will the presence of the unmodified recipient be monitored?'** may generate the answer, 'It will not be monitored.' Alternatively, if some monitoring is planned, application of the guide work NONE would envisage that for some reason or another the intended monitoring was not carried out. Although neither of these cases suggests there would be much activity to consider, the consequences of the lack of monitoring should be considered.

Step 3: Examine each consequence, decide whether it is sufficiently serious to require action to be taken to avoid it and, if so, whether it has a realistic cause

7.15 The consequences of each deviation are assessed to decide whether or not they are acceptable. If a consequence of a possible deviation is not acceptable then the question is asked whether, taking into account the safety procedures already in place, there is a mechanism by which it might possibly happen. If so, then action must be taken to prevent it.

7.16 In many cases the evaluation of the deviation or consequence in a qualitative manner within the GENHAZ study will be adequate. However GENHAZ, like HAZOP, is a technique for identifying hazards and not a procedure for quantifying the risk that may be consequent on a given hazard. It may be desirable to evaluate quantitatively, as a separate exercise, some of the consequences that might be generated in the course of a GENHAZ study using risk assessment techniques. These could be done by the GENHAZ team themselves or external assessors could be commissioned to carry out the analysis and report back to the study team (see paragraph 7.20). Equally it may be possible to identify hazards so transparently unacceptable that an immediate decision can be made to seek ways of eliminating the hazard (see Step 4).

Step 4: Decide what action should be taken

7.17 Action recommended by the GENHAZ study team may range from a call for further information to proposals for specific additional safety measures or even to a recommendation that the release proposal should be abandoned. The team might have sufficient expertise to be able to make proposals for avoiding some unacceptable hazards but in other cases the recommended action may be to refer the hazard back to the release team to consider changes in procedure or other aspects of the plan. Alternatively there may be a need to refer the suggested deviation to an expert in a field not represented in the GENHAZ team. It is of course possible that the decision will be that no action is required. Whatever the decision the GENHAZ team must make clear in the record what action is recommended and who should implement it.

7.18 The question of who should decide what hazards have no realistic cause and what consequences are unacceptable arises in GENHAZ as in other investigations into safety. In HAZOP it is usually a team from the company proposing the project that undertakes the study and makes recommendations for action. Similar circumstances will normally apply with GENHAZ. The record of the information and discussion generated in the study, together with recommended actions, should provide an excellent record of the process that has led to the decisions. This document could serve as a basis for review by others, for example, the Advisory Committee on Releases to the Environment.

Step 5: Implementation and reference back to the GENHAZ team

7.19 A senior person, who may or may not be part of the GENHAZ team, should have responsibility for seeing that the recommended actions are implemented, or that there is good reason why they are not.

7.20 If the actions include research into questions raised during the study, there will be a need for further GENHAZ team meetings to review the outcome of that research. Similarly, if the proposals were referred back to the release team for review, the modified proposals and revised statements of intent should be re-submitted to the GENHAZ team for assessment. These

subsequent meetings of the GENHAZ team are part of the GENHAZ study and should be recorded and reported in the same way as the initial study, preferably in the same document, although there may be occasions when an interim report is required. The follow-up work is not strictly complete until all the agreed actions have been implemented.

Throughout: Maintain an audit trail

7.21 One of the beneficial characteristics of the GENHAZ procedure is that its systematic nature facilitates the logical recording of assessments of the deviations, consequences, causes and actions. This is invaluable, since maintaining an audit trail in this way allows reassessment of the study at a later date and by other interested parties if this should prove useful. For example, if something unexpected did happen, despite the careful carrying out of a GENHAZ study, then the release team (or other investigators) could work back through the records of the GENHAZ study to see whether the event had been considered, enabling them to report on what lessons might be learned for future studies. Alternatively if, before the release, grave doubts were expressed about its safety, the proposals and the GENHAZ study report could be re-examined to check that due weight had been given to the points of doubt.

CHAPTER 8

A HYPOTHETICAL GENHAZ STUDY

Introduction

8.1 In this chapter an indication is given of the lines of thought generated by applying four of the guide words to a PRODUCT at the stage MAKE or SELECT in a hypothetical field trial of a genetically engineered potato. It is not possible, within the scope of this report, to present by way of example more than an indication of the pattern of the method and the way in which the guide words give rise to trains of thought. The entries under the various headings are far fewer and briefer than would be the case in an actual study. Moreover, the analysis is not taken through to the point at which risks are assessed and precautionary measures, if needed, are defined.

The hypothetical experiment

8.2 The potato plant in the hypothetical experiment is to be modified by the insertion of a gene coding for an imaginary protein (TP) that is toxic to a specific caterpillar pest. The gene has a promoter that results in its expression in leaves. This gene is transferred together with a gene conferring resistance to the antibiotic, kanamycin. This last gene enables cells containing the added construct to be selected from other unmodified cells during the preparation in the laboratory of the genetically modified plant. The gene also serves as a useful marker for the inserted gene constructs. The purpose of the release is to assess the efficacy of the modification in protecting the potato from the caterpillar and to look for other effects, both favourable and adverse, on the growth of the plant and the quality of the crop.

8.3 The following pages indicate, using the sequential format for recording a GENHAZ study (Figure 7.2), how the GENHAZ approach might be used for such an experiment.

Record of GENHAZ study

Title of study: *Hypothetical project* Date:

Team membership: *Chairman*
Recorder
Others

Project leader:

Submitting organisation:

Hypothetical project (continued)

Stage: MAKE or SELECT Component: PRODUCT

Question 1.3.1: *By what means will the construct be inserted into the recipient, and how many copies will be inserted, to make the product?*

Answer 1.3.1: *The genes will be introduced through a wound in a segment of the potato leaf or tuber, by contact with a bacterium containing a plasmid as the vector, and are expected to be incorporated into the plant genome. Whole potato plants will then be produced by tissue culture of the plant cells selected in the presence of kanamycin and will be planted out in the trial. We do not know how many copies of the construct will be inserted.*

Guide word: *MORE – (a) more copies of genes;*

– (b) greater expression of genes.

Deviation: *(1) More genes stabilised in the potato genome than intended.*

Consequences: *More potential for gene transfer to other plants or for deletion?*

Causes: *(1) More copies in the bacterial plasmid.*

(2) Potato plant infected by several plasmid-containing bacteria.

(3) Gene replicated before integration in the plant genome.

(4) Gene replicated after integration..

Actions: *(1) Consider this possibility under sections 5.2 and 5.3 of the questionnaire: Gene Transfer – Construct and Product.*

(2) Determine the amount of transferred DNA accurately.

Deviation: *(2) More TP in the potato plant than intended.*

Consequences: *(a) The potato plant might be toxic to a wider range of species than is intended.*

(b) There might be a reduction in the production of other proteins essential to the potato plant.

Causes: *Greater expression of the TP gene.*

Actions: *See overleaf.*

Actions

For consequence (a), consider:

(i) What is the susceptibility of organisms, other than the target organism, to TP?

(ii) Is the potential risk of harm to any organism that feeds on the plant (including decomposer organisms) important? (see also section 7.3 of questionnaire: Termination and Clean-Up – Product).

(iii) If so, what factors, other than the numbers of transferred genes and the degree of expression of the genes, govern the concentration of TP in the plant?

(iv) Is TP found in other parts of the plant, apart from the leaves? If so, where, and at what concentration? (See also guide word WHERE ELSE).

(v) Is enough known about the TP levels overall and in various tissues in the treated potato plants? Is there sufficient information concerning the susceptibility of organisms that might come into contact with TP in the plants?

(vi) Can the amount of DNA that is introduced be accurately controlled? (see also action (2) for deviation (1)).

(vii) Does the amount or concentration of TP vary during plant development? If so, this must be taken into consideration if the concentration of TP is measured.

(viii) How will the above considerations affect the reliability and predictive value of the results of the trial?

For consequence (b), consider:

(i) The likelihood of an essential metabolic pathway being pre-empted, or the availability of a limiting factor being reduced, by the production of TP, leading to the production of fewer essential proteins. Devise means of monitoring such effects during the trial.

(ii) Should a deliberate overdose of construct be included in the trial to assess whether the production of proteins would be restricted by a high concentration of TP?

Deviation:

(3) Increased activity of the TP gene in a particular tissue. (See also guide word WHEN ELSE*).*

Consequences:

As for deviations (1) and (2).

Causes:

Different action of the promoter, or increased activity of the promoter in a specific tissue, or reduced turnover of TP.

Actions:

Consider what consequences could result from:

(1) A change in TP activity in the plant overall or in particular tissues.

(2) The possibility of heightened TP activity in subsequent generations of the potato plant due to promoter instability.

Reference: MAKE or SELECT / PRODUCT / 1.3.1 (continued)

Guide word:	PART OF – *(a) only part of the intended genetic material is added;* – *(b) only part is expressed.*
Deviation:	*(1) The whole TP gene might not be inserted or might not be expressed.*
Consequences:	*Erroneous conclusions would be drawn from the trial.*
Causes:	*(1) Whole TP gene not inserted into the bacterial plasmid.*
	(2) Loss of TP gene or part of it from the plasmid before or after inoculation, or during transfer to the plant genome.
Actions:	*Will the presence of the complete TP gene be verified in all plants?*
Deviation:	*(2) The marker gene might not be inserted or might not be active.*
Consequences:	*If it were the intention to rely solely on the presence of the marker gene to identify released plants, then plants without this gene could escape detection.*
Causes:	*As for deviation (1), substituting 'marker gene' for 'TP gene'.*
Actions:	*Consider:*
	(i) Whether the presence of the marker is essential to the trial. If so, are there techniques for detecting the marker gene?
	(ii) The implications of the loss of the marker gene from the potato plant, eg from natural processes.
Deviation:	*(3) The promoter might not be inserted or might not be active.*
Consequences:	*(1) The TP gene would not be expressed and, consequently, TP would not appear in the leaves (or any other part of the plant).*
	(2) TP might appear in tissues other than the leaves, if it is expressed by another promoter or mutant promoter.
Causes:	*As for deviation (1), substituting 'promoter' for 'TP gene'.*
Actions:	*For consequence (1), see action for deviation (1).*
	For consequence (2), consider under the guide word WHERE ELSE.

Reference: MAKE or SELECT / PRODUCT / 1.3.1 (continued)

Guide word:	OTHER THAN
Deviation:	*Genetic material other than that intended might be introduced into the genome of the potato plant.*
Consequences:	*Unpredictable.*
Causes:	*Contamination of the construct or bacterium.*
Actions:	*(i) Review the possibility that genetic material other than that intended, could be introduced to the potato plant.*
	(ii) Identify potential contaminants and consider the precautionary measures to prevent contamination or mistaking one construct for another.

Guide word:	WHERE ELSE
Deviation:	*(1) The TP gene might be expressed in another part of the plant besides the leaves.*
Consequences:	*(a) Other regions of the plant, apart from the leaves, might become toxic to non-target organisms. For example:* *Roots and tubers: Toxic to humans, soil organisms?* *Hairs: urticaceous if TP is in the plant hairs? Cultivated potatoes are not normally hairy but there is a wild hairy type which is highly pest resistant and is used in breeding.* *Pollen: Would pollen containing TP be poisonous to bees or induce an allergic reaction in humans or other animals?* *Nectar: Would nectar containing TP produce toxic honey?* *(b) TP might concentrate in a tissue other than the leaves.*
Causes:	*The TP gene and promoter might have mutated to be active in another region of the plant.*
Actions:	*For consequences (a) and (b), consider:* *(i) What might come into contact with, or eat, the different parts of the plant.* *(ii) The mode of action of TP on both the target and non-target organisms, including humans.* *(iii) The toxicological information on proteins similar to TP.*
Deviation:	*TP might be present in dead caterpillars.*
Consequences:	*These caterpillars might be toxic to predators or decomposer organisms.*
Causes:	*The caterpillars have ingested the leaves containing TP which is lethally toxic to them.*
Actions:	*Consider this possibility and its implications.*

CHAPTER 9

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Purpose

9.1 Our Thirteenth Report recognised the importance of a systematic and penetrating search for potential hazards in the release to the environment of genetically engineered organisms, now more widely referred to as genetically modified organisms (GMOs). We drew attention to a procedure known as HAZOP (Hazard and Operability Study) that had proved very successful in identifying possible hazards, in particular in the chemical industry.

9.2 The Commission set up a small Working Party to explore the feasibility of adapting HAZOP to the release of GMOs. The Working Party devised a workable variant which was called GENHAZ.

9.3 The Commission has now developed GENHAZ as far as it reasonably can. Further development needs to take place in the context of full trials of GENHAZ on real proposals for release. This report is intended to provide sufficient material to undertake such trials and we recommend that the Government with the assistance of its Advisory Committee on Releases to the Environment (ACRE) should arrange for these to take place. The trials will, no doubt, suggest further modifications to the procedure. In the light of that experience and of advice from ACRE the Government should consider whether to integrate GENHAZ into the procedures for risk assessment of GMO releases and, if so, should prepare a users' manual drawing on this report and the outcome of the trials. In the light of the international interest in risk assessment of GMO releases, the Government should also take steps to encourage other countries to explore the use of GENHAZ. (paragraph 1.6)

9.4 It will be desirable, should GENHAZ receive official acceptance, to develop an agreed standard procedure and then to make only agreed modifications. (paragraph 1.7)

9.5 We recommend that the Government should consider whether modifications might be necessary for application to proposals in areas such as genetically engineered vaccines and to proposals for releases of GMOs in commercial products. (paragraph 1.8)

9.6 A full GENHAZ study, like HAZOP, can require two to three weeks or more. Suggestions were made during the development of GENHAZ for simplifying the procedure in ways which might reduce the time required. We consider that a compressed procedure should not be adopted unless it has been proved in trials to be as effective as the full exercise. (paragraph 1.9)

9.7 It is to be expected that each laboratory will learn from its GENHAZ studies and, where appropriate, modify its practices to eliminate sources of risk which might occur in future projects. In addition, in the application of GENHAZ, general points will emerge that could sensibly be incorporated in advice on good practice for the design and implementation of release proposals. We recommend that the Government should review from time to time the outcome of GENHAZ studies to identify such general points and ensure that they are incorporated in appropriate advice documents. (paragraph 1.10)

9.8 Very few releases will be exact replications of others. We therefore recommend application of GENHAZ to every proposal. (paragraph 1.10)

9.9 Both HAZOP and GENHAZ must be applied to detailed, definitive plans. However, in the trials of GENHAZ it became clear that its additional application at an early stage in the planning of a release could generate perceptions that could significantly improve smooth running and the value of the results of a release experiment. GENHAZ is thus an effective tool for planning as well as for uncovering potential hazards. (paragraph 1.11)

HAZOP

9.10 Safety in the design of industrial plant for chemical manufacture relies on the application of design codes which are based on the wide experience and knowledge of professionals in the industry. This may not be adequate to identify and deal with all hazards that may arise. This recognition led to the development of HAZOP as an additional step in the pursuit of safety. HAZOP looks at the consequences of failure to control the operation of a chemical plant within its intended limits, asking what would happen if something unintended were to occur despite the safety mechanisms and procedures already built in.

9.11 HAZOP takes as its starting point a representation, often in diagrammatic form, of the *INTENTION* for the construction and operation of the proposed plant. HAZOP uses *GUIDE WORDS* to focus attention on possible *DEVIATIONS* from what was planned. For each deviation possible *CAUSES* and *CONSEQUENCES* are worked out. If the deviation is judged to have both a realistic cause and hazardous consequences, *ACTION* to deal with the hazard is considered.

From HAZOP to GENHAZ

9.12 It became apparent to the Working Party that the diagrammatic representation of the manufacturing plant used as the basic input to a HAZOP study was not a convenient way of expressing the construction and release of a GMO. Even if it were, the information would be presented in a format that would not be consistent with patterns of thinking familiar to biologists. Moreover, the impact of the release of a living organism includes the possibility of mobility and replication of both organism and genes, adding a dimension that is not present in the case of a lifeless product. An alternative means of expressing the intentions was developed in a way which would enable it to encompass the behaviour and interactions of the living organisms concerned. It covered all stages of a project and considered the impact of all the components of the genetically modified organism. It was subsequently augmented by answers to a structured questionnaire. Further minor modifications to the HAZOP approach were made as described in Chapter 4.

9.13 A GENHAZ study could last two to three weeks, or longer if re-examination of some aspects were required. However, the importance of identifying all serious hazards, not to mention the saving in getting things right first time, will far outweigh the time spent on the exercise.

9.14 The current set of questions in the questionnaire could probably be improved. It may well be that the set would need to be modified for some releases. (paragraph 4.13)

The GENHAZ procedure in outline

9.15 The main elements of the GENHAZ framework are shown in outline in Figure 5.2 on page 15. Three COMPONENTS are distinguished in the

genetically modified system which is the subject of the release. These are termed CONSTRUCT, RECIPIENT and PRODUCT. Seven stages of the release process are defined. These are:

MAKE or SELECT
RELEASE
ESTABLISH
POPULATION
GENETIC TRANSFER
MONITOR
TERMINATE AND CLEAN UP

9.16 The GENHAZ questionnaire is laid out in 7 sections corresponding to the stages of the release. Within each section groups of questions relate to each of the components of the genetically modified system. The questionnaire is set out in full on pages 22–27.

9.17 As each stage of the release is considered, the guide words are applied one by one to answers to the questionnaire to suggest ways in which outcomes may depart from the plan. The complete list of guide words is given in Figure 5.3 on page 17. The steps in a GENHAZ study are set out in Figure 5.4 on the same page. The procedure is explained in detail in Chapters 6 and 7. Chapters 5–7 are in effect a handbook for those who may wish to take GENHAZ further.

Answering the questionnaire

9.18 The answers to the questionnaire, the statements of intent, will provide a description of the release proposal. They will describe what is to be done in preparation for the release and during the release itself, what is expected to happen as a result and the factors that are likely to affect what happens. Since the answers to the questionnaire provide detailed statements of the intentions of the proposal, this part of the process should be completed by the release team before the start of the formal GENHAZ exercise but when the design of the release is complete. Any changes made in the design after the questionnaire is answered will compromise the GENHAZ exercise, which must be carried out on the final design. If changes to the intended procedure are made subsequent to the completion of the GENHAZ study, then all statements of intent that are changed must be re-examined by the GENHAZ procedure.

9.19 However, experience has shown that it can also be very useful to the release team to answer the questionnaire and carry out an initial GENHAZ study before the design of the experiment is finalised. This can lead to improvements in the design. The questionnaire can then be answered again after finalising the design in preparation for the main GENHAZ study.

The GENHAZ study team at work

9.20 A GENHAZ study is undertaken by a team working together rather than by individuals. The team should include scientists from all relevant disciplines and should be drawn mainly from those who have planned and will carry out the release. The study requires a team leader who is familiar with the operation of GENHAZ but who does not need to be a specialist in the subject of the release.

9.21 While it would be helpful if the whole GENHAZ team were experienced in the procedure, the team leader and those team members keeping the record, as a minimum, should undergo some training prior to the start. It would be beneficial if a third person, who would play the role of prompter, could also receive some training. If GENHAZ becomes part of the pro-

cedures for risk assessment, then we recommend that the Government, with the advice of its Advisory Committee on Releases to the Environment, should develop a training programme for GENHAZ team leaders and other participants. (paragraph 7.6)

9.22 The team leader must have a plan for the progress of the study and must arrange the necessary meetings. A working record of the study can be kept in a tabular form or in a sequential form. Examples of these two formats are provided in Figures 7.1 and 7.2 on pages 30 and 31.

9.23 The study team begins its work by applying the guide words to activities or events that are specified or implicit in the statements of intent described in the responses to the questionnaire. Applying the guidewords will suggest deviations from the intentions. It may prove effective to consider groups of questions and answers together. The GENHAZ team must consider carefully the implications of the deviations generated by applying the guidewords in order to uncover the possible consequences of the release not going according to plan.

9.24 The consequences of each deviation are assessed to decide whether or not they are acceptable. If a consequence is not acceptable then the question is asked whether, taking into account the safety procedures already in place, there is a mechanism by which it might possibly happen. If so, then action must be taken to prevent it. The team must make clear in the record what action is recommended and who should implement it.

9.25 A senior person should have responsibility for seeing that the recommended actions are implemented or that there is good reason why they are not. The actions may require reference back to the GENHAZ team if they involve, for example, research into questions raised during the study or modification of the release proposal and of the statements of intent. These subsequent meetings are part of the GENHAZ study and should be recorded in the same way. The follow-up work is not strictly complete until all the agreed actions have been implemented. (paragraph 7.20)

9.26 The systematic nature of the GENHAZ procedure facilitates logical recording of assessments of deviations, consequences, causes and actions. Maintaining an audit trail in this way allows reassessment of the study at a later date.

A hypothetical GENHAZ study

9.27 Chapter 8 indicates how the GENHAZ approach might be used for a hypothetical experiment to modify a potato plant.

Acknowledgement

We are indebted to all those who have helped with the development of GENHAZ. They are listed in Appendix 2. We would particularly like to thank Keith Powell, whose inspiration provided the essential structure for the GENHAZ development. We are also grateful to Trevor Kletz, who gave the working party a thorough introduction to HAZOP, and to Dick Flavell and his colleagues at the John Innes Institute, who arranged for the working party a trial of GENHAZ on one of their experiments and participated so effectively. We should like to single out for special mention one of our number, Charles Suckling, without whose guidance and contribution this report could not have been produced. Finally we should like to thank our Secretary, Brian Glicksman, and Assistant Secretary, Pat Green, who made important personal contributions to this report.

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

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June 1991

APPENDIX 1

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APPENDIX 2

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The Royal Commission would like to thank all those who contributed to the development of GENHAZ

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Dr D Tyrrell	Chairman, Advisory Committee on Dangerous Pathogens
Dr P Young	Applied genetics dept, John Innes Institute; biological safety officer

GLOSSARY AND ACRONYMS

Glossary

Antibiotic	A substance, produced by micro-organisms, that destroys or inhibits the growth of other organisms.
Bacterium	A single-celled organism which does not have a nuclear membrane.
Chromosome	A dense cellular structure, made up of DNA and protein molecules, along which genes are located.
Copy number	The number of copies of a given gene present in a cell.
Decomposer organism	An organism that obtains energy from the chemical breakdown of dead organisms or animal or plant waste.
DNA	Deoxyribonucleic acid, which is present in all living cells and contains the information for cellular structure, organisation and function.
Donor	An organism whose genetic material, cells, tissues or organs are transferred to another (the recipient).
Ecological niche	The status or role of an organism in its environment. An organism's niche is defined by the types of food it eats, its predators and other factors.
Enzyme	A protein that changes the rate of a biological reaction.
Expression	The process of producing proteins using the information contained in genes.
Gene	The unit of hereditary, 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.
Genetic engineering	Genetic engineering is concerned with deliberately changing the genes of an organism in order to alter one or more of its characteristics. (Refer to paragraphs 2.12 to 2.16 in the Royal Commission's Thirteenth Report for a more detailed explanation.)
Genetics	The study of heredity and variation between organisms.
Genome	All the DNA contained in a single set of chromosomes of an organism.
Germination	The initial stages in the growth of a seed to form a seedling.
Host range	The variety of organisms (hosts) which another organism can exploit for nourishment and shelter.
Inoculation	Insertion of a substance or organism into another organism, or the transfer of an organism to a medium.

Nucleic acid	Complex molecules found in cells. The two 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.
Pathogenic	Disease-causing.
Pest	An organism having a destructive association with another organism. Such organisms are frequently an economic or medical nuisance to man.
Plasmid	A loop of DNA, in bacteria and certain other organisms, that exists and replicates independently of the chromosomes.
Pollen	The grains containing the male sex cells (gametes) of seed plants.
Promoter	The part of a gene that regulates its expression ie production of proteins.
Protein	A chemical, consisting of chains of amino acids, that controls the function and structure of cells.
Recipient organism	An individual which receives genetic material, cells, tissues or organs from the body of another.
Recombinant DNA (rDNA)	DNA that has been modified by joining together different pieces of DNA using the techniques of genetic engineering rather than by traditional methods.
Restriction enzymes	Enzymes, produced by many micro-organisms, which cleave foreign DNA. They are an important tool in genetic engineering for cutting DNA.
Tissue	A collection of similar cells organised to carry out one or more particular functions.
Tissue culture	The growth of the tissues of living organisms outside the body in a suitable culture (nutrient) medium.
Trophic level	The position that an organism occupies in a food web (complex set of feeding relationships).
Tuber	A swollen underground stem or root in certain plants eg the potato is a stem tuber.
Urticaceous	Stinging like a nettle.
Vascular plant	A plant possessing organised tissues which conduct water and nutrients through the plant body.
Vector	An organism or substance (loop of DNA in this case) that carries an organism or substance (in this case, a gene) to another organism.
Virus	A non-cellular particle composed of a protein shell and a nucleic acid core. It can reproduce only in living cells.
Wild type	The form of a gene which is usually found in nature.

Acronyms

ACDP	Advisory Committee on Dangerous Pathogens
ACGM	Advisory Committee on Genetic Modification (formerly the Advisory Committee on Genetic Manipulation)
ACRE	Advisory Committee on Releases to the Environment
GMO	Genetically Modified Organism
HAZOP	Hazard and Operability Study
HSE	Health and Safety Executive
ICI	Imperial Chemical Industries PLC
OECD	Organisation for Economic Co-operation and Development
RCEP	Royal Commission on Environmental Pollution

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Index

This index covers the text of the report and does not contain entries for the contents of the GENHAZ Questionnaire (Chapter 6) or the hypothetical study (Chapter 8).

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