Department of Health

Report on Health and Social Subjects

38

Guidelines on the Assessment of Novel Foods and Processes

Advisory Committee on
Novel Foods and Processes

HMSO

Department of Health

Report on Health and Social Subjects

38

Guidelines on the Assessment of Novel Foods and Processes

Advisory Committee on
Novel Foods and Processes

London: HMSO

First published 1991

ISBN 0 11 321336 0

Preface

Dramatic advances have been made in recent years in food biotechnology and, in particular in techniques for genetic modification. This is likely to result in a significant number of novel foods and foods produced by novel processing becoming available for consumption by man in the years to come.

My Committee was reconstituted in 1988 to provide an independent expert forum for the scientific evaluation of the safety of such foods. This was not a novel venture for advice on the safety assessment of novel foods was produced by our predecessor Committee in 1984. However, it was felt that with the reconstitution of the Committee and the recent scientific developments, now was an appropriate time to revise and update such guidance to those wishing to develop and/or market novel foods in this country. It was for this reason that my Committee has produced these Guidelines, which we hope will be useful to companies involved in this area.

DEREK C BURKE
Chairman

Contact Point

Anyone wishing to obtain further information on these Guidelines, or advice on making submissions to the Advisory Committee on Novel Foods and Processes should in the first instance contact the Administrative Secretary:

Ms C Brock
Room 609
Eileen House
80/94 Newington Causeway
London SE1 6EF

Contents

Chapter 1 Introduction

Remit of ACNFP

1.1 The Advisory Committee on Novel Foods and Processes (ACNFP) is an independent body of experts whose remit is:

> 'to advise Health and Agriculture Ministers of Great Britain and the Heads of the Departments of Health and Social Services and Agriculture for Northern Ireland on any matters relating to the irradiation of food or to the manufacture of novel foods or foods produced by novel process, having regard where appropriate to the views of relevant expert bodies'.

1.2 The 'expert bodies' referred to above include the Panel on Novel Foods of the Committee on Medical Aspects of Food Policy; the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment; and the Advisory Committee on Genetic Modification. These bodies are all represented on the ACNFP. The ACNFP also liaises with other Committees, such as the Food Advisory Committee (FAC) and the Advisory Committee on Releases to the Environment (ACRE)—See para 5.44. The FAC is responsible for a number of areas including food labelling, food composition and food additives. Although the FAC has responsibility for advising on food additives, it consults the ACNFP on those additives produced using the techniques of **genetic modification***. The working relationship of ACNFP to various other committees is given in Figure I. The background to the formation of ACNFP is given below.

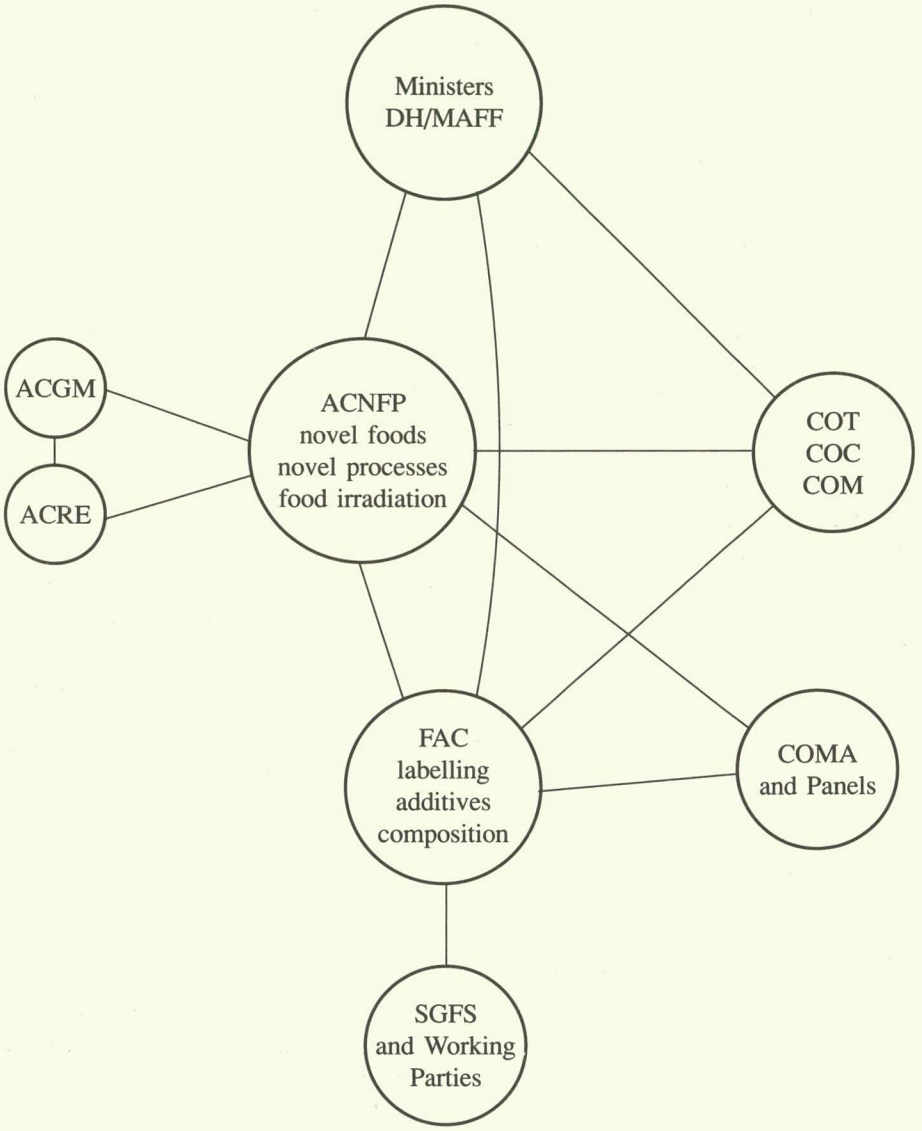
Predecessor Committee

1.3 As a result of an understanding reached with the Ministry of Agriculture, Fisheries and Food (MAFF) in 1980, the then Food and Drink Industries Council (FDIC) invited its member associations to recommend that their member companies notify MAFF before marketing a novel food, so that the nutritional and safety aspects of the food might first be evaluated, in strict confidence, by independent experts. This understanding reflected a recommendation of the Food Standards Committee in its 'Report on Novel Protein Foods', (HMSO, 1974).

1.4 Subsequent to this understanding being reached, Ministers appointed the Advisory Committee on Irradiated and Novel Foods (ACINF) with a remit to advise on the irradiation of food and on the safety of novel foods or foods produced from novel processes.

*Terms in bold are explained more fully in the Glossary.

Figure 1. ACNFP—Lines of communication



COT	Committee on Toxicity
COC	Committee on Carcinogenicity
COM	Committee on Mutagenicity
FAC	Food Advisory Committee
SGFS	Steering Group on Food Surveillance
ACGM	Advisory Committee on Genetic Modification
ACRE	Advisory Committee on Releases to the Environment
COMA	Committee on Medical Aspects of Food Policy

1.5 Most of the work of ACINF related to the evaluation of food irradiation and a report was issued on this topic in 1986 (Report on the Safety and Wholesomeness of Irradiated Foods) with a Response to the comments received on the Report being issued in 1987. ACINF, as well as giving advice on certain food projects submitted by the food industry also issued a 'Memorandum on the Testing of Novel Foods' in 1984, which included guidelines for the testing of novel foods.

Reconstitution as ACNFP

1.6 Following the completion of the review of food irradiation by ACINF, and bearing in mind the significant advances in recent years in food **biotechnology** and in particular, in techniques for genetic modification, Ministers decided to reconstitute the Committee as the Advisory Committee on Novel Foods and Processes (ACNFP) in 1988. The Committee's new name better reflects its future work which includes the assessment of the safety of foods which are themselves genetically modified **organisms** or which are produced in processes involving such organisms, although the Committee continues to advise as necessary on food irradiation. The membership of the Committee was increased to strengthen its expertise in biotechnology and genetic modification, whilst retaining its expertise in the more traditional areas of nutrition, microbiological safety, chemical toxicology and biophysics/radiobiology. A full membership list is given as Appendix A.

Guidance on information requirements for assessment of novel foods and processes

1.7 As well as giving advice to Ministers on submissions on individual novel foods and processes, the work of ACNFP includes giving guidance to the food industry on the sort of information it would wish to see in any such submission. In order to fulfil this aspect of its work, the ACNFP has updated and revised the Guidelines issued by ACINF in 1984 to take account of the wider range of novel food products now being submitted for assessment and the newer techniques of genetic modification.

Chapter 2 Definition of Novel Foods and Processes

2.1 A food may be novel as a result of the use of novel raw materials, novel processing or preparation techniques or novelty of its role in the diet. Novel food organisms or products derived from such organisms may result from recently developed techniques such as genetic modification or from more conventional plant and animal breeding techniques. It is unlikely that an all-embracing definition for novel foods and processes covering all eventualities can be derived and therefore the following definitions have been established, together with explanatory notes which attempt to delineate the extremes of products to be included in the definitions of novel and to identify those products falling outside the definitions:

—'Novel foods are foods or food ingredients which have not hitherto been used for human consumption to a significant degree in the United Kingdom and/or which have been produced by extensively modified or entirely new food production processes'.

—'A novel process is a process which has not hitherto been used in the processing of foods'.

2.2 This definition of a novel food used by the ACNFP in its operation of the current voluntary scheme covers all foods intended for UK consumers which may be marketed in a form or manner that could bring about significant food safety or nutritional changes in the diet. This excludes food additives, including flavourings and processing aids, but not living organisms added to food, such as starter cultures. Components extracted from conventional foods by traditional processes, recipe changes or minor process modifications are not considered to be novel, though any significant nutritional implications would be of relevance to the Committee.

2.3 Prior to their introduction, products such as mycoprotein, faba bean isolate, and rapeseed oil are foods which would have been regarded as novel foods.

2.4 The definition of a novel process is intended to cover processes which could bring about significant toxicological or nutritional changes in the food. Prior to their introduction, the processes of freeze-drying, pasteurisation, extrusion and irradiation are examples of what would have been regarded as novel processes. However, small temperature changes or changes to the design of a process vessel would not be regarded as novel.

2.5 Under current UK food law, companies must be satisfied of the safety of their products and should themselves evaluate whether foods or processes should be referred to the Committee for consideration. Manufacturers should be aware that even minor changes in a process may have significant consequences. While it is not possible to give comprehensive guidance on the type of products or processes to be referred, food produced by technology such as genetic modification and synthetic food items such as certain fat replacers will be of particular interest.

2.6 The use of new food species, or of novel varieties obtained by outbreeding traditional crop varieties with wild types or exotics, may in some instances raise novel problems of nutrition or toxicology and in such cases would be evaluated by the Committee.

Chapter 3 Legislative Position

3.1 The clearance scheme described in these guidelines operates under voluntary arrangements which have developed from an agreement between the Department of Health, Ministry of Agriculture, Fisheries and Food and the then Food and Drink Industries Council in 1980. The Food Safety Act, 1990 contains provisions that would enable the voluntary scheme to be put on a statutory basis. In addition, the European Commission are expected to make proposals to regulate novel foods on a Community basis in the near future. It is envisaged that a companion document to these Guidelines will be issued in due course, describing the legislative position in greater detail, and also including guidance on the notification procedures arising from the legislation.

Chapter 4 Strategy for Assessment

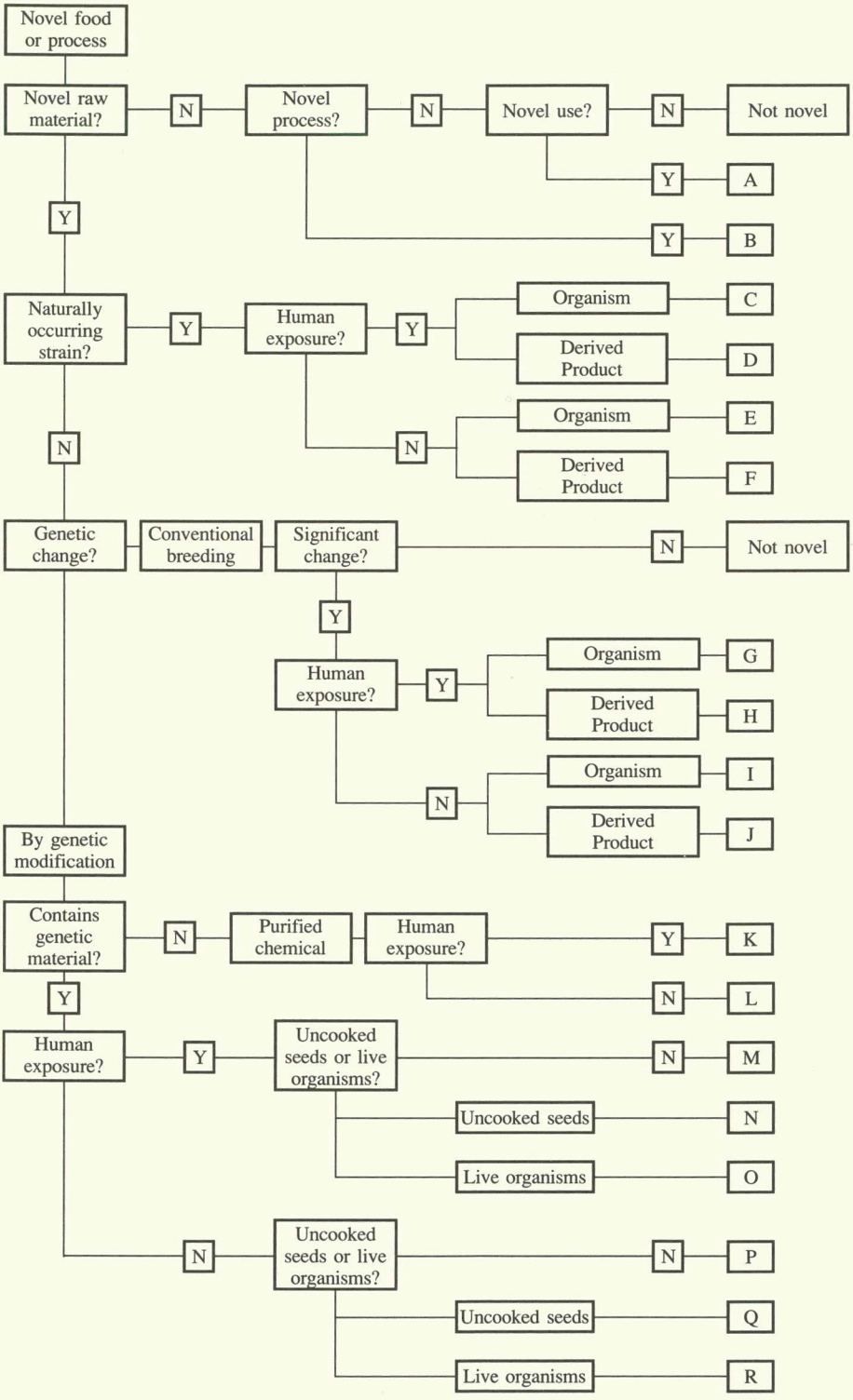
General considerations

4.1 The term 'novel food' can encompass many different types of material, ranging from a selected strain of an existing food organism to a new strain obtained by traditional breeding techniques, or as a result of genetic modification procedures. However, new varieties of plants are evaluated by the Plant Variety Rights Office. This evaluation, whilst primarily to determine whether the new variety has unique and stable agronomic characteristics, can also take into account impact on consumers. Therefore the ACNFP will concentrate its attention on novel foods produced other than by traditional plant breeding and the decision tree at page 8 reflects this emphasis.

4.2 The novel food may be the organism itself, be it a micro-organism, plant or animal (or a part thereof), or it may be a product dervied from such an organism. A novel food product may be equivalent to an existing product but be produced by an extensively modified or entirely new process, for example a food component previously extracted from plants now being produced from a **recombinant** micro-organism. Existing foods may also be subjected to novel processes.

4.3 With such a wide range of considerations, it is obvious that the need for assessment and the amount of information necessary for such an assessment will vary from one example to another. Therefore, in order to provide guidance for those producing such foods or those wishing to market them, the Committee has derived a decision-tree scheme which, by answering a series of questions, will indicate the types of information likely to be required in individual situations. It is emphasized that this scheme is designed to give guidance only and that it is *not* a rigid checklist. The Committee wishes to stress its flexible approach to the assessment of novel foods and processes and its willingness to consider reasoned arguments as to why certain information may or may not be relevant in individual cases.

DECISION-TREE



Key to Decision Tree

Exit Point	Information Requirements
A	V
B	III, IV, V, VIII
C	I, II, III, V, IV
D	I, II, III, IV, V, VI
E	I, III, V, VI, VIII, IX
F	I, III, IV, V, VI, VIII, IX
G	I, II, III, V, VI, VII
H	I, II, III, IV, V, VI, VII
I	I, III, V, VI, VII, VIII, IX
J	I, III, IV, V, VI, VII, VIII, IX
K	I, II, III, IV, V, VI, VII, VIII, X, XII
L	I, III, IV, V, VI, VII, VIII, IX, X, XII
M	I, III, V, VI, VII, VIII, X, XI, XII, XIII
N	I, III, V, VI, VII, VIII, X, XI, XII, XIII, XIV
O	I, III, VI, VII, VIII, X, XI, XII, XIII, XIV, XV
P	I, III, V, VI, VII, VIII, IX, X, XI, XII, XIII
Q	I, III, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV
R	I, III, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV

The numbers I–XV above refer to the information requirements listed below. These are described in greater detail in Chapter 5 to these Guidelines.

I. —Instructions for use
II. —Evidence of previous human exposure
III. —Intake/extent of use
IV. —Technical details of processing and product specification
V. —Nutritional studies
VI. —History of organism
VII. —Characterisation of derived strain
VIII. —Toxicological assessment
IX. —Human studies
X. —Assessment of a genetic modification procedure
XI. —Effect of a genetic modification procedure on the known properties of the parent organism
XII. —Genetic stability of a modified organism
XIII. —Site of expression of any novel genetic material
XIV. —Transfer of the novel genetic material
XV. —Assessment of a modified organism for survivability, colonisation and replication/amplification in the human gut.

Note: **Conventional breeding** includes **non-specific mutagenesis** and any other techniques not included in the term genetic modification.

Decision tree

4.4 A schematic representation of the decision tree, which covers both novel foods and processes is given on pages 8–9. The intention of the tree is to indicate the information requirements for the different categories of novel foods or processes. For novel foods this will include the techniques used in their production; any previous history of human exposure to the parent organism(s); and the intended use (the organism itself or a **derived product**). A further important consideraton is whether the material in question is likely to be a significant dietary item, either in terms of total intake or as a source of a particular macro or micronutrient.

4.5 In cases where a novel food has been derived using genetic modification procedures, a further question is whether or not the novel food product contains modified genetic material. If it does, then it is also important to determine the state in which this modified genetic material is likely to be consumed, as this will determine its capability to be transferred either to the consumers of the food or their gut flora. The different categories would be:

(i) cooked products and the raw flesh of fruits and vegetables whose seeds are not eaten, such as peaches or carrots;

(ii) uncooked fruits and vegetables containing edible seeds, such as strawberries, tomatoes and cucumbers;

(iii) live organisms, such as those present in live yogurts or in unpasteurised beers.

Novel food or process categorisation

4.6 Working through the decision tree scheme will result in a novel food or process categorisation A to R. Each of these has varying information requirements (I–XV, as indicated on the scheme). Some examples of novel foods and processes that have been put through the decision tree, together with their categorisation and resulting information requirements, are given in Appendix B. These information requirements are described in more detail in Chapter 5 of these Guidelines. Again it is emphasized that these are not rigid requirements and that there is expected to be a degree of flexibility when considering an individual submission.

Chapter 5 Information Requirements

5.1 Foods are labelled so as to inform the consumer of their true nature. This is important for reasons of consumer choice and particularly so where there may be a personal history of allergic or intolerance reactions to particular foods or food components. Labelling matters are part of the remit of the Food Advisory Committee (FAC). In order to assist it in its consideration of labelling matters for genetically modified foods, the FAC has provided guidelines to be applied in each case. To help those developing such novel food products a copy of the FAC's current guidelines is included at Appendix C. However, these guidelines may need to be reviewed in the light of experience with particular products. It is recommended that a check be made with the Administrative Secretary of the FAC[1] to obtain the most up-to-date advice on the labelling of all novel foods, including those produced using the techniques of genetic modification.

5.2 The need for informaton on the aspects described in the following sections I–XV will depend on the particular novel food or process in question and should be determined by reference to the decision tree scheme as given in Chapter 4.

I. Instructions for use

5.3 Some novel food products may require particular preparation or cooking conditions to ensure their safety, such as the need for a period of vigorous boiling for certain dried beans. The inclusion of appropriate instructions for use will be necessary for such foods.

II. Evidence of previous human exposure

5.4 Reliable, high quality information on any previous history of human exposure to a novel food elsewhere in the world should be included in a submission in support of the safety of either the novel food organism or of products derived from such organisms. This should include data on amounts consumed and patterns of intake and of any preparation/cooking of the material before consumption. However, anecdotal evidence will be given little weight. Information on the history of human exposure will be particularly important where there are traditional handling or cooking requirements for a food novel to the UK. This information will need to be made available to con-

1. Administrative Secretary of FAC, Ministry of Agriculture Fisheries and Food, Room 504C, Ergon House c/o Nobel House, 17 Smith Square, London SW1P 3JR.

sumers as, for example, is the advice regarding the necessity for a minimum period of vigorous boiling when cooking various dried beans.

III. Intake/extent of use

5.5 Submissions should include information on the potential market as indicated by the particular properties of the food. For food products derived from novel sources, information on the range of applications for the product and the levels of use for each application will be necessary. It will also be important to estimate the potential intake in terms of both the average consumer and also any particular subgroup(s) of the population that might consume extreme amounts of the food for whatever reason. However, account should be taken of any marketing limitations that might be imposed by the projected scale of production facilities.

5.6 The submission should also give consideration to any existing foods in the diet that might be displaced, so that any resultant nutritional implications could be assessed, such as the need for micronutrient supplementation or fortification.

IV. Technical details of processing and product specification

5.7 Any novel processing/preparation techniques used to produce a novel food should be described, as such processing/preparation may result in microbiological hazards and/or the generation of toxic products or in nutrient losses. In situations where the novel food is a product derived from a novel organism, a detailed specification for the product will be necessary. Whilst it may be possible to give a chemical specification for the product in some instances (eg relatively simple substances such as citric acid), this may not be possible for a complex food component (such as an oil with a varied triglyceride pattern). In such cases, a detailed description of the method by which the product is obtained should be included in the submission and this should form the basis of a 'process specification' for the product. Evaluation of a process will include an analysis of the process per se and the identification of critical points which might lead, for example, to microbiological contamination or nutrient loss. A number of foods most likely to be produced by the novel process will be evaluated as if they were novel foods.

5.8 In addition, the source of a novel food product may indicate potential problems. Thus novel foods produced from plant materials may need to be examined for the presence of particular natural toxins or antinutritional factors. Novel foods produced from marine products may need examination for heavy metals and toxins. Novel fats or oils should be examined for unusual fatty acids such as erucic acid. Production processes involving microorganisms may indicate the need for examination for the potential to produce toxins or pathogens. If a novel protein product is functionally, but not structurally, the same as an existing protein with an established safety-in-use,

then that safety-in-use history may not be relevant to the novel protein, and additional testing might be required eg for immunotoxicological effects.

5.9 Although the source material used to produce a novel food may be of a 'food-grade' standard, it will still be important to determine the levels of potential contaminants such as herbicides, pesticides, veterinary medicines or environmental contaminants in the starting materials as such contaminants could be concentrated in the novel food product during processing.

5.10 Where genetic modification procedures have been used to obtain a source organism for a novel food product, particular attention will have to be given to the consequences of that genetic change (see paras 5.34–5.44).

5.11 The specification provided should allow assessment of the limits within which the manufacture of the product is controlled. It should include details of product variability and of analytical methods and sampling procedures used to check the specification.

5.12 If the application relates to a production on a pilot scale (which seems likely to be the usual situation), the company will have to demonstrate that when produced in a larger scale plant the food will be nutritionally and toxicologically consistent in all respects with that cleared and that each batch will comply with the pilot scale specification(s). Clearance of a novel food or process will usually be conditional upon compliance with the product and/or process specifications of the material to which the test data relate and possibly upon the inclusion of further criteria within the specification(s). Evidence from batch production may not be relevant to continuous production.

5.13 If the crude protein, total fat or carbohydrate constitutes a significant amount of the dry matter of a food (say 10%), these components may need to be more fully investigated in absolute terms, as well as for possible interactions between constituents, as follows:

(a) Crude protein may need to be examined for the true protein and non-protein nitrogenous material. Individual amino acids may need to be determined as may unusual and toxic amino acids if their presence is suspected. Non-protein nitrogenous components such as nucleic acids and amino-glycosides may need to be determined.

(b) Total fat may need to be examined for saponifiable and non-saponifiable components. A full fatty acid spectrum may need to be determined. Particular attention should be paid to the presence of phospholipids, sterols, cyclic fatty acids and known toxic fatty acids and the amounts of saturated, mono-unsaturated and poly-unsaturated fatty acids. This could include an assessment of fatty acids with trans double bonds in the monoenoic and polyenoic fractions; *cis,cis,*9,12-octadecadienoic acid and fatty acids with chain lengths of 22 and over, both mono- and polyenoic; together with peroxidised and degradation products of polyunsaturated fatty acids.

(c) Total carbohydrate may need to be examined for its content of sugars, oligosaccharides and polysaccharides. The oligosaccharides and poly-

saccharides may need to be characterised with respect to their susceptibility to hydrolysis by alpha-amylase, pattern of individual monomers (including amino-sugars) and their linkages.

5.14 A novel food should be analysed for the presence of toxic metals (eg lead, arsenic etc). Depending on its intended use, analysis for metals of nutritional significance (eg iron, zinc, calcium) may be appropriate.

5.15 The vitamin content should be determined if the presence or absence of particular vitamins is likely to be nutritionally significant (see para 5.18).

5.16 If the nature of the novel food or the novel process indicates the possible presence of naturally occurring or adventitious antinutritional factors (eg phytate, trypsin inhibitors etc) or toxins (eg haemagglutinins, mycotoxins etc), the product should be analysed for them specifically, by chemical techniques in the first instance. Biological tests, either as part of the nutritional evaluation in the case of enzyme inhibitors or more specifically as part of a mycotoxin screening programme, will provide useful back-up evidence concerning the presence or absence of these contaminants.

5.17 The results of such analyses, will need to be evaluated in their own right and also in comparison with the appropriate existing foods or food components.

V. Nutritional evaluation

5.18 The nutritional evaluation of a novel food will be particularly important for those products expected to become of major dietary significance. The nutritional consequences for the diet should be assessed both at normal and maximum probable levels of consumption particularly in respect of groups such as children, the elderly and those dependent on institutional catering, and those who may be especially susceptible to the particular nature and compostion of the food. This is to include those such as phenylketonurics who could suffer adversely, or might benefit from a novel food. The nutrient content should be assessed by chemical analysis, taking account of storage, further processing and cooking. The effects of any anti-nutritional factors (eg inhibitors of enzyme activity or mineral metabolism) on the nutrient content of the whole diet should also be assessed. Animal studies may need to be carried out to determine metabolisable energy, protein quality, if appropriate, and vitamin and mineral **bioavailability** from both the food and diets containing the food. If a food is expected to have an important role in the diet, animal experiments should be validated with appropriate studies in humans.

VI. History of organism

5.19 The history of an organism can provide information that is important to the assessment of a novel food. There may be a history of toxin production by certain strains, species or genera and it would be important in such cases to examine the particular strain of the organism being used for the potential

to produce such toxins, both under the conditions used in normal manufacturing and also under extreme conditions. Immuno-chemical and other tests exist for a number of known toxins. A variety of non-specific biological tests have been investigated for the purpose of screening for unknown toxins produced by a particular organism but generally have not been found to be helpful. However, it is possible that the use of relevant **gene probes** to screen for the presence of sequences capable of producing toxins may provide a more effective and specific method for determining whether an organism has the potential to produce toxins known to be associated with related species or genera.

5.20 Strain selection or conventional breeding techniques, as well as influencing the toxin-producing capacity of an organism, may also influence positive nutritional factors such as vitamin levels or the proportions of unsaturated fatty acids and information on these aspects should also be provided. Breeding for disease resistance may increase the concentration of resistance factors which may be toxic to mammals as well as to unwanted species and the chemical identity of these should be investigated.

VII. Characterisation of derived strain in comparison with the parent strain

5.21 Where an organism has been altered, whether by conventional breeding techniques or by genetic modification procedures, the relationship of the derived strain to the parent(s) should be characterised, particularly with respect to growth requirements, potential for toxicity and pathogenicity, genetic stability and variety of products (see also paras 5.36–5.38).

VIII. Toxicological assessment

5.22 When carrying out any toxicological testing, it is important that the material being tested complies with the same specification as that to be marketed (see para 5.12). This will usually be the uncooked food; additional toxicological data on the cooked food may also be necessary if, for example, cooking inactivates or removes naturally-occurring toxins (see para 5.3).

5.23 As explained in the following paragraphs, special considerations apply in toxicological testing, especially when foods might constitute a significant proportion of the human diet. In particular:

(a) The traditional method of assessing the safety of a food additive, ie allowing a one hundred-fold margin between the maximum amount of the additive likely to be consumed in the human diet and the maximum amount which has no toxic effect when fed to animals, clearly cannot be applied to a food which would constitute more than one per cent of the human diet. In any case, there are practical limits to the amounts of certain foods which can be included in animal diets without adversely affecting the animals' nutritional status and health. Due to the complex

nature of foods there is a need to balance test and control diets for both major and minor components.

(b) A food, once it has been adequately tested in appropriate animal and *in vitro* systems, may need to undergo tolerance testing, including monitoring for possible allergenicity (see paras 5.31–5.32).

5.24 The general principles of animal husbandry to be adopted when assessing the safety of foods are set out in the DHSS 'Guidelines for the Testing of Chemicals for Toxicity' (HMSO, 1982). This document should also be consulted for further details of the tests discussed below.

5.25 Before starting animal studies, it is desirable to investigate the nutritional properties and the palatability of the test diet in the test animals. If a palatability problem is encountered, it may be necessary to increase the amount of food to the required level gradually. Paired-feeding techniques should be used if the problem cannot be overcome.

5.26 As foods are usually complex mixtures of chemicals, studies on the metabolic fate of every constituent of the food would be impracticable. However, if it is suspected that contaminants or minor components are a cause of toxicity, the metabolism of the suspect chemicals should be investigated. It may be relevant in some situations to investigate the digestibility of the novel food material. Also, if a novel food, or a major component of it, consists of a new chemical compound which does not normally occur in the diet (eg a novel carbohydrate), studies of the metabolic fate after ingestion of the new compound will be appropriate.

5.27 Changes in normal excretory functions caused by a food may be relevant, and analysis of urine and faeces may give important information. For example, a novel food may alter the gut flora drastically, or may encourage preferential loss of a mineral or vitamin to the detriment of the good health of the study animals.

5.28 As a novel food will usually consist mostly of compounds unlikely to produce acute toxic effects (carbohydrates, lipids and proteins), acute toxicity studies will normally be inappropriate.

5.29 In most instances where some toxicological testing of a food is necessary, this will consist, at least initially, of a 90-day repeated dose study, normally in the rat, and a battery of *in vitro* mutagenicity screening tests. If the extent of human exposure to the food is likely to be widespread and the intake significant, then further toxicological studies will also be required, such as tests for chronic toxicity/carcinogenicity, embryotoxicity (including teratogenicity) and effects on reproduction. Details on the performance of such studies is given in the DHSS 'Guidelines for the Testing of Chemicals for Toxicity' (HMSO, 1982). There are problems in the interpretation of mutagenicity tests on foods, particularly in view of the presence of numerous mutagens in naturally-occurring foodstuffs. Nevertheless, such studies may be

valuable and will be needed on some novel foods. Their interpretation may be aided by comparison with conventional foods. The DH 'Guidelines for the Testing of Chemicals for Mutagenicity' (HMSO, 1989) details the 'basic package' of recommended tests. The *in vitro* mutagenicity testing of some novel foods may present particular technical problems, owing to the presence in the growth medium of nutrients from the food. Similarly, some products derived from novel food organisms, such as proteins or oils, may also interfere with the various *in vitro* test systems. Thus it may be necessary to use special bacterial strains or cell lines or suitable extraction procedures prior to testing.

5.30 It is recognised that there are difficulties in interpreting animal studies (particularly those in the rat) on foods, due to differences in gastrointestinal tract function and other related matters between animals and man; for example differences in microflora, coprophagia etc.

IX. Human studies

5.31 There is a wide diversity of types of studies that may need to be performed in humans on novel foods or products derived from novel foods, including the tasting of a new variety of an existing food organism, large scale acceptability and marketing trials and tests for intolerance or allergenicity. These studies in man are to confirm acceptability and tolerability, not to investigate potential toxicity. The ethical and legal considerations of studies in human subjects have been discussed elsewhere ([1,2,3]). Such considerations are particularly important when testing novel foods because of benefit/risk considerations.

5.32 The following types of studies may be appropriate:

—tasting/palatability;
—single dose/short term repeated dose studies for digestibility and tolerance;
—allergenicity, including observations of any allergic reactions in occupationally exposed personnel;
—acceptability/marketing trials.

5.33 The Committee is in the process of drawing up guidelines on the conduct of taste trials on foods produced using the techniques of genetic modification. In the meantime, advice for those wishing to conduct such trials may be obtained from the ACNFP Secretariat.

---

1. DHSS. 'Guidelines for the testing of chemicals for toxicity'. London. HMSO, 1982. (Report on Health and Social Subjects; 27).
2. Royal College of Physicians. 'Research on Healthy Volunteers'. Journal of the Royal College of Physicians. Vol. 20 no. 4 p1–17. October 86.
3. Royal College of Physicians. 'Guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects'. Second Edition. The Royal College of Physicians of London. January 1990.

X. Assessment of a genetic modification procedure

5.34 In situations in which an organism has been altered using genetic modification techniques, the safety assessment of the organism itself, or that of any product derived from such an organism, will centre on the nature of the genetic modification. Any such submission should include detailed information on the following aspects:

—identification and characterisation of the **host** organism, including the strain and the site of the modification;

—the nature of the modification, the source of the inserted material and its purity, including the genetic and metabolic relationship between the host organism and the new material, and the stability of the **insert** within the **genome**;

—the method of insertion, including details of the **vector** used, the identity of any **linker segments** or additional **stop codons** and the amount of vector nucleic acid remaining in the modified organism;

—the relationship of the insert with various controlling elements in the genome;

—the method of selection of the modified organisms with the appropriate transplanted **gene(s)**, including confirmation of the sequence of the **cloned** gene and details of any **resistance markers** used. If the markers code for resistance to drugs in clinical use then evidence that they have been jettisoned or suitably inactivated will normally be necessary;

—if the modification is a **deletion**, how this was achieved together with checks on the specificity of the deletion, as well as any potential effects this might have on upstream or downstream controlling sequences.

XI. Effect of a genetic modification procedure on the known properties of the parent organism

5.35 As well as information on the genetic modification procedure itself, a submission should also include information on any effects of that procedure on the known properties of the host organism. This will include any effects on the toxin-producing capacity of the organism under both normal and extreme conditions, as well as any effects on positive nutritional factors such as vitamin levels. For example, with a genetically modified strain of potato it would be important to determine levels of solanine, as well as levels of vitamin C, both in the potato as harvested and consumed and after extremes of storage; comparison with the non-modified strain may be helpful.

XII. Genetic stability of a modified organism

5.36 It is important to determine the **genetic stability** of the organism following modification. For micro-organisms it will be important to determine the stability of the organism on storage prior to use in any fermentation, and

the establishment of a **seed pool** or deposition of the modified organism with an established repository is required. However, it is accepted that there may be strong commercial reasons for not adopting the latter course. The establishment of a seed pool would involve storage in more than one place and each pool should be sufficiently large so as to be able to generate enough product for at least one years use.

5.37 The stability of a genetically modified micro-organism will also need to be determined under normal production conditions. The number of generations monitored should be in proportion to the number of generations expected in a normal production run. Such tests may include measurement of the production of the desired product by the micro-organism (for example levels of enzyme activity) and also analyses of **DNA** to show the presence, status and **copy number** of the inserted gene within the DNA of the host organism.

5.38 Testing for the genetic stability of modified plants and animals will also be required.

XIII. Site of expression of any novel genetic material

5.39 In higher organisms a gene may be inserted which it is intended should only be expressed in a particular part of the organism, for example a gene conferring increased pest resistance which is to be expressed only in the leaves of a plant or a gene for an important human protein such as a blood-clotting factor which is directed for expression only in the mammary gland of an agricultural animal so that the desired protein can be harvested from the milk. In such cases it will be important to determine that the gene is not expressed elsewhere, such as the fruit of the plant or the meat of the animal.

5.40 Some micro-organisms may be genetically modified to produce important biological materials, either at specific stages of their growth only, or only in the presence of specific agents or substrates; for example, brewers yeast which is normally discarded after separation from beer may be modified to produce other materials following a change of substrate. Again, it will be important to determine that the gene is not expressed under other conditions, such as are used in normal food manufacturing procedures.

XIV. Transfer of novel genetic material

5.41 There is little evidence to suggest the transfer of genetic material from higher organisms, such as fruit to human consumers or to gut flora, and any such transfer would not be only from genetically modified organisms but would be a general problem. However, genetic material transferred to higher organisms via **viruses** might be mobilisable and information would be needed on this potential. Little is known about the potential transfer to man of DNA from dead food micro-organisms but any potential for transfer to gut microflora would need to be assessed. For live genetically modified micro-

organisms, such as in live yogurts, it may be necessary to assess the likelihood of any transfer of the novel genetic material to the normal gut flora.

XV. Assessment of a modified organism for survivability, colonisation and replication/amplification in the human gut

5.42 In cases where fermented foods containing live genetically modified organisms are consumed raw, such as live yogurts or beers, it may be important to assess the modified organisms for its ability to survive in the human gastro-intestinal tract, to colonise the gut and for replication/amplification of the organism to occur within the gut. It may also be important to assess the immune response to such colonisation and to determine whether there is any significant generation of the relevant gene products within the gut.

5.43 It will also be important to determine any effect of the modified organism on the existing/normal gut flora populations, including any nutritional implications of this for the host.

5.44 Under present UK and EC legislation the consequences of any survival of genetically modified organisms in the general environment is not within the remit of this Committee. Such aspects will be considered by the Advisory Committee on Releases to the Environment (ACRE).

Chapter 6 Data Deposition

6.1 The ACNFP recommends that as much as possible of the data it considers be published or otherwise made available for public scrutiny. The Committee accepts the difficulties involved in publishing studies with negative findings and has therefore instituted a scheme for deposition of such data in the British Library under its Supplementary Publications Scheme. This is similar to the already existing scheme for data on food additives. The Committee also accepts that some of the information made available to it will be commercially sensitive (eg marketing and process details) and thus should not be so deposited. Companies making submissions will be asked to indicate whether they would be unwilling for any of the data made available to the Committee in support of their submission to be deposited in such a scheme.

Glossary

The terms in bold in the text are explained more fully below:

Bioavailability — is a term used to describe the extent to which a food component can be utilised within a living organism and may be less than the actual amount present.

Biotechnology — is the application of biological organisms, systems or processes to manufacturing and service industries.

Chromosome — is a self-replicating structure consisting of DNA complexed with various proteins and is involved in the storage and transmission of genetic information; it is the physical structure that contains the genes.

Clone

1. A clone is a group of genetically identical cells or organisms derived from a single common ancestor.
2. Clones are genetically modified replicas of DNA sequences.

Conventional breeding — is the selection of particular offspring arising from sexual reproduction.

Copy number — is the number of times a particular coding sequence is present in the DNA molecule.

Deletion — is a structural change resulting in the loss of a section of the genetic material and the genetic information contained therein.

Derived product — is that product not containing genetic material, obtained from an organism which is used as a food or food ingredient.

DNA — is deoxyribonucleic acid, which is present in all living cells and contains the information for cellular structure, organisation and function.

Gene — is the unit of heredity composed of DNA, which forms part of a **chromosome**.

Gene probe — is a biochemical tool that is designed to react specifically with a particular gene, or part of a gene, thereby identifying the presence of that gene or part of a gene in the genetic make-up of an organism or cell.

Genetic modification — is the propagation of combinations of heritable material by the insertion of that material, prepared by whatever means outside a cell or organism, into a cell or organism in which it does not occur naturally, either directly or indirectly via a virus, microbial **plasmid** or other vector system which can then be incorporated into the cell or organism.

Genetic stability — is the degree to which the genetic make-up of a micro-organism or cell is inherited unaltered by subsequent generations.

Genome — is the sum total of the genes of an organism.

Host — is an organism into which has been introduced heritable genetic material prepared elsewhere.

Insertion — is the addition of one or more **nucleotide base** pairs into a DNA molecule.

Linker segment

1. is a short DNA segment containing the recognition site for a specific **restriction enzyme**.
2. is a short piece of DNA used to link together an inserted segment of DNA and the host DNA into which it has been inserted.

Non-specific mutagenesis — is the process of mutation of an organism or cell by techniques not included in the term genetic modification. This would include methods such as the use of mutagenic chemicals, or ionising or UV irradiation.

Nucleotide bases — are strung along the sugar-phosphate 'backbones' to form the nucleic acids DNA and **RNA**. DNA has 4 such bases; adenine, cytosine, guanine and thymine. These bases form specific pairs, adenine always pairing with thymine and cytosine always pairing with guanine. In RNA uracil replaces thymine.

Organism — is any living thing, including a virus.

Plasmid — is a loop of DNA in bacteria and certain other organisms, that exists and replicates independently of the chromosomes.

Recombinant DNA — is DNA that has been altered by joining together different pieces of DNA using the techniques of genetic modification rather than by conventional breeding methods.

Resistance marker — is a DNA sequence conferring resistance to a particular chemical normally toxic to the cell or organism, such as an antibiotic or herbicide.

Restriction enzymes — are produced by many bacteria to cleave foreign DNA in the bacteria. This cleavage is at specific sites and thus such enzymes are important tools in genetic modification for cutting DNA.

RNA — is ribonucleic acid; this exists in several functional forms, which together are responsible for converting the information contained in genes into the active chemicals (proteins). RNA can also be the hereditary material in certain viruses.

Seed pool — is an 'in-house' long term store of the first production strain of an organism used commercially, which is kept for reference purposes.

Stop codon — is a set of three consecutive nucleotide bases signalling the termination of the process whereby DNA is copied to form RNA.

Vector — is a self-replicating DNA molecule that transfers a DNA segment between host cells.

Virus — is a non-cellular particle composed of a protein shell and a nucleic acid core. It can reproduce only in living cells.

Appendix A: Membership of the Advisory Committee on Novel Foods and Processes

Chairman

Professor D C Burke, BSc, PhD, HonLLD

Members

Professor G E Adams, BSc, PhD, DSc, FACR
Professor A T Atkinson, BSc, PhD
Dr A C Baird-Parker, OBE, BSc, PhD
Professor W P T James, MA, MD, DSc, FRCP, FRCP (Edin), FRSE
Professor B E Moseley, BSc, PhD
Professor D J Naismith, BSc, PhD
Professor P Richmond, BSc, PhD, DSc, CPhys FInstP
Dr P J Rodgers, MA, DPhil
Professor J E Smith, BSc, MSc, PhD, DSc, FIBiol, FRSE
Dr J W G Smith, MD, FRCP, FRCPath, FFPHM, FIBiol, DipBact
Professor D A T Southgate, BSc, PhD, MIBiol
Dr A J Swallow, PhD, DSC, ScD, CChem, FRSC
Professor P Turner, MD, BSc, FRCP, FFPM
Professor R Walker, PhD, FRSC, CChem, FIFST

Dr A N B Stott, MB, ChB, FFOM was a member of the Committee from its reconstitution in 1988 until 18.4.90.

Secretariat

Medical	—	Dr R Singh, BSc, MBChB, MSc, Dip SAD
Scientific	—	Dr D Jonas, BSc, PhD
Administrative	—	Ms C Brock

The following officials also served as members of the Secretariat during the preparation of these Guidelines.

Mr K Dale	October 1988 – February 1989
Mr P Otley	October 1988 – September 1989
Mrs M Fry	September 1989 – August 1990

Appendix B: Examples of novel foods and processes that have been put through the decision tree

1 *Simplesse*

questions:	novel raw material?	— No
	novel process?	— No
	novel use?	— Yes
	Therefore A—information requirements	— *v*

2 *Irradiation*

questions:	novel raw material?	— No
	novel process?	— Yes
	Therefore B—information requirements	— *iii,iv,v,viii*

3 *Fructose Syrup containing Dextrans*

questions:	novel raw material?	— Yes
	naturally occurring strain?	— Yes
	history of human exposure?	— Yes
	organism or derived product?	— derived product
	Therefore D—information requirements	— *i,ii,iii,iv,v,vi*

4 *Mycoprotein*

questions:	novel raw material?	— Yes
	naturally occurring strain?	— Yes
	history of human exposure?	— No
	organism or derived product?	— derived product
	Therefore F—information requirements	— *i,ii,iii,iv,v,vi, viii,ix*

5 *Oil from micro-organism*

questions:	novel raw material?	— Yes
	naturally occurring strain?	— No
	genetic change?	— by conventional breeding
	significant change?	— Yes
	history of human exposure to parent organisms(s)	— Yes
	organism or derived product?	— derived product
	Therefore H—information requirements	— *i,ii,iii,iv,v,vi,vii*

6 *Enzyme from genetically modified organism*

questions:	novel raw material?	— Yes
	naturally occurring strain?	— No
	genetic change?	— by genetic modification
	contains genetic material?	— No (purified chemical)
	history of human exposure to host organism?	— Yes
	Therefore K—information requirements	— *i,ii,iii,iv,v,vi, vii,viii,x,xii*

or

	history of human exposure to host organism	— No
	Therefore L—information requirements	— *i,iii,iv,v,vi,vii, viii,ix,x,xii*

7 *Genetically modified tomato*

questions:	novel raw material?	— Yes
	naturally occurring strain?	— No
	genetic change?	— by genetic modification
	contains genetic material?	— Yes
	history of human exposure to host organism?	— Yes
	does the food contain uncooked seeds or live organisms?	— Yes (uncooked seeds)
	Therefore N—information requirements	— *i,iii,v,vi,vii,viii, x,xi,xii,xiii,xiv*

8 *Genetically modified bakers yeast*

questions:	novel raw material?	— Yes
	naturally occurring strain?	— No
	genetic change?	— by genetic modification
	contains genetic material?	— Yes
	history of human exposure to host organism	— Yes
	does the food contain uncooked seeds or live organisms?	— Yes (live organisms)
	Therefore O—information requirements	— *i,iii,vi,vii,viii, x,xi,xii,xiii,xiv, xv*

Appendix C: Guidelines for the Labelling of Foods Produced Using Genetic Modification

The Food Advisory Committee has been considering the role which genetic engineering is beginning to play in food production and has been concerned to identify those uses of the technology which could present moral and ethical concerns for some consumers. The Committee has concluded that there are some uses of the technology in the production of food which would generate such concerns because of the possible presence of genetically modified organisms[1] (GMOs) in the final food. The Committee felt that labelling was not the answer to these concerns except where the presence or use of GMOs could be considered to alter materially the nature of the food. The Committee concluded that under these circumstances specific food labelling should be used to inform consumers of the use of gene technology. The Committee has designated four basic food categories as a primary screening mechanism to determine when specific food labelling is required. These four food categories which have formed the basis of the Guidelines for the Labelling of Foods Produced Using Genetic Modification, have been developed to assist the Committee with its own work. Therefore it should not be assumed that the labelling advice for each of the four categories would automatically apply in every case. The Committee wishes to consider the labelling requirements for such foods on a case-by-case basis and as a consequence these guidelines may then need to be revised. The four categories of the primary screen are defined below:

i. *Nature Identical Food Products of GMOs*

Foods which are the products of, or which contain products of, a genetically modified organism (but not the organism itself, its cells or DNA) which are identical to products from conventional organisms traditionally consumed in Western Europe.

This category refers only to the use of products of a genetically modified organism in food and not the organism itself, its cells or its DNA, and furthermore restricts itself to products which are identical to those which are traditionally consumed in Western Europe and are derived by conventional methods from conventional materials. In this case the Committee already has a precedent. When this Committee considered the case of need for the enzyme chymosin, produced from the transfer of the calf chymosin gene to a micro-organism, it was concluded that because the product, bacterial chymosin B, was indistinguishable from calf chymosin B, it would be unnecessary to require special labelling provisions. The Committee confirmed this view as a general principle for this category of products.

ii. *Food from Intra-species GMOs*

Foods which are or which contain a genetically modified organism (or its cells and/or DNA) which is produced only from the gene pool of its own species.

In this category the process of genetic modification can be said to represent a more rapid and effective alternative to selective breeding programmes for achieving the required characteristics of the organism. The Committee felt that in the majority of cases in this category, special labelling would be unnecessary, but each case should be considered on its merits. The essential point for consideration was whether the consumer was likely to be misled, or might wish to be informed. The Committee when subsequently asked to consider special labelling provisions for a genetically modified bakers yeast, which resulted from the insertion of a gene from another variety of yeast, decided that this organism clearly fell into this category and that it was not necessary to apply special labelling provisions to the bread which contains it.

iii. *Novel Food Products of GMOs*

Foods which are the products of, or which contain products of a genetically modified organism (but not the organism itself, its cells or DNA) which differ from products from conventional organisms traditionally consumed in Western Europe.

The products in this category are not identical to products currently in the diet from conventional organisms. They may include for example novel fats, proteins or carbohydrates produced by GMOs. The Committee stated that as a general principle special labelling of food which contains these products of GMOs would probably be required.

iv. *Foods from Trans-species GMOs*

Foods which are or which contain a genetically modified organism (or its cells and/or DNA) which is produced by the introduction of genetic material from any source other than the same species as the host organism, excluding non-functional short chain DNA linker sequences.

The Committee generally felt that the greatest potential source of public concern about genetically modified organisms lies with this category, since the incorporation of genes from one species into a host organism of a different species represents a departure from that which can be achieved by conventional breeding practices. It was recognised that the end-product, a trans-species genetically modified organism, would provide a focus of moral and ethical concern for some consumers and that sufficient information should be provided through food labelling in order that consumers can choose to avoid such products if they wish. The Committee's recommendations on the labelling of foods, which have been subjected to irradiation were cited as an example of such an approach. For cases falling into this category, the Committee therefore agreed to the principle that there would probably be a need for labelling in *all* cases to allow consumers to distinguish foods made from these organisms from foods made with conventional organisms, however, the Committee will consider each case on its merits. The Committee accepted that although foods from trans-species GMOs would normally require specific labelling, where such GMOs derive from closely related species which already produce fertile

off-spring by natural means, eg a GMO loganberry from blackberry and raspberry parents, an exception might be made, but that such decisions would be made on a case-by-case basis.

The Form of the Labelling Declaration

When consumers should be informed about the use of GMOs and their products in, or as foods, the Committee has decided that the following statement should be made as part of the labelling requirements:

'(contains) products of gene technology'

and that when an ingredient of the food is a product of gene technology, this should also be identified in the ingredients list.

---

1. For the purposes of this document the term genetically modified organism is defined as:

'organisms in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination'.

Included within the definition are the following techniques:—

(a) recombinant DNA (r-DNA) techniques using vector systems as previously covered by Council Recommendation 82/472/EEC. [ie the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside the cell, into any virus, bacterial plasmid or other vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation].

(b) techniques involving the direct introduction into a (micro-) organism of heritable material prepared outside the (micro-) organism including micro-injection, macro-injection and micro-encapsulation.

(c) cell fusion or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

Techniques which are not considered to result in genetic modification on the condition that they do not involve the use of r-DNA molecules or GMOs are:

(a) *in vitro* fertilisation

(b) conjugation, transduction, transformation or any other natural process

(c) polyploidy induction

For the purposes of this document the following techniques are not considered to result in genetic modification, provided that they do not involve the use of GMOs as recipient or parental organisms:

(a) mutagenesis

(b) cell fusion (including protoplast fusion) of cells from plants which can be produced by traditional breeding methods.

Printed in the United Kingdom for HMSO
Dd293557 1/91 C25 G443 10170

DH RHSS 38 Guidelines on the Assessment of Novel Foods and Processes HMSO

HMSO publications are available from:

HMSO Publications Centre
(Mail and telephone orders only)
PO Box 276, London, SW8 5DT
Telephone orders 071-873 9090
General enquiries 071-873 0011
(queuing system in operation for both numbers)

HMSO Bookshops
49 High Holborn, London, WC1V 6HB 071-873 0011 (counter service only)
258 Broad Street, Birmingham, B1 2HE 021-643 3740
Southey House, 33 Wine Street, Bristol, BS1 2BQ (0272) 264306
9-21 Princess Street, Manchester, M60 8AS 061-834 7201
80 Chichester Street, Belfast, BT1 4JY (0232) 238451
71 Lothian Road, Edinburgh, EH3 9AZ 031-228 4181

HMSO's Accredited Agents
(see Yellow Pages)

and through good booksellers

ISBN 0-11-321336-0

9 780113 213368

£4.25 net