ANNEX 1

TERMS OF REFERENCE

To advise at the request of:

Food Standards Agency
Department of Health
Ministry of Agriculture, Fisheries and Food
Department of the Environment, Transport and the Regions
Department of Trade and Industry
Health and Safety Executive
Medicines Control Agency: Section 4 Committees and the Licensing Authority
Scientific Advisory Committee on Nutrition
Home Office
Scottish Executive
National Assembly for Wales
Northern Ireland Executive
Other Government Departments

1. To assess and advise on the toxic risk to man of substances which are:

   a. used or proposed to be used as food additives, or used in such a way that they might contaminate food through their use or natural occurrence in agriculture, including horticulture and veterinary practice or in the distribution, storage, preparation, processing or packaging of food;

   b. used or proposed to be used or manufactured or produced in industry, agriculture, food storage or any other workplace;

   c. used or proposed to be used as household goods or toilet goods and preparations;

   d. used or proposed to be used as drugs, when advice is requested by the Medicines Control Agency, Section 4 Committee or the Licensing Authority;

   e. used or proposed to be used or disposed of in such a way as to result in pollution of the environment.

2. To advise on important general principles or new scientific discoveries in connection with toxic risks, to co-ordinate with other bodies concerned with the assessment of toxic risks and to present recommendations for toxicity testing.

ANNEX 2

CODE OF CONDUCT FOR MEMBERS OF ADVISORY COMMITTEES

Public service values

Members must at all times:

- observe the highest standards of impartiality, integrity and objectivity in relation to the advice they provide and the management of this Committee;

- be accountable, through the Chairman of the Food Standards Agency, the Chief Medical Officer, to Ministers, Parliament and the public for its activities and for the standard of advice it provides.

The Ministers of the sponsoring departments are answerable to Parliament for the policies and performance of this Committee, including the policy framework within which it operates.

Standards in Public Life

All Committee members must:

- follow the Seven Principles of Public Life set out by the Committee on Standards in Public Life (see below);

- comply with this Code, and ensure they understand their duties, rights and responsibilities, and that they are familiar with the function and role of this Committee and any relevant statements of Government policy. If necessary members should consider undertaking relevant training to assist them in carrying out their role;

- not misuse information gained in the course of their public service for personal gain or for political purpose, nor seek to use the opportunity of public service to promote their private interests or those of connected persons, firms, businesses or other organisations; and

- not hold any paid or high profile unpaid posts in a political party, and not engage in specific political activities on matters directly affecting the work of this Committee. When engaging in other political activities, Committee members should be conscious of their public role and exercise proper discretion. These restrictions do not apply to MPs (in those cases where MPs are eligible to be appointed), to local councillors, or to Peers in relation to their conduct in the House of Lords.

Role of Committee members

Members have collective responsibility for the operation of this Committee. They must:

- engage fully in collective consideration of the issues, taking account of the full range of relevant factors, including any guidance issued by the Food Standards Agency; the Department of Health and sponsor departments or the responsible Minister;

- in accordance with Government policy on openness, ensure that they adhere to the Code of Practice on Access to Government Information (including prompt responses to public requests for information); agree an Annual Report; and, where practicable and appropriate, provide suitable opportunities to open up the work of the Committee to public scrutiny;

- not divulge any information which is provided to the Committee in confidence;

- ensure that an appropriate response is provided to complaints and other correspondence, if necessary with reference to the sponsor department; and

- ensure that the Committee does not exceed its powers or functions.

Individual members should inform the Chairman (or the Secretariat on his or her behalf) if they are invited to speak in public in their capacity as a Committee member.

Communications between the Committee and the Food Standards Agency (FSA) Board and /or Ministers will generally be through the Chairman except where the Committee has agreed that an individual member should act on its behalf. Nevertheless, any member has the right of access to the FSA Board and/or Ministers

on any matter that he or she believes raises important issues relating to his or her duties as a Committee member. In such cases the agreement of the rest of the Committee should normally be sought.

Individual members can be removed from office by the FSA Board if they fail to perform the duties required of them in line with the standards expected in public office.

The role of the Chairman

The Chairman has particular responsibility for providing effective leadership on the issues above. In addition, the Chairman is responsible for:

- ensuring that the Committee meets at appropriate intervals, and that the minutes of meetings and any reports to the FSA Board accurately record the decisions taken and, where appropriate, the views of individual members;
- representing the views of the Committee to the general public; and
- ensuring that new members are briefed on appointment (and their training needs considered), and providing an assessment of their performance, on request, when members are considered for re-appointment to the Committee or for appointment to the board of some other public body.

Handling conflicts of interests

The purpose of these provisions is to avoid any danger of Committee members being influenced, or appearing to be influenced, by their private interests in the exercise of their public duties. All members should declare any personal or business interest which may, or may be *perceived* (by a reasonable member of the public) to, influence their judgement. A guide to the types of interest that should be declared is below.

(i) Declaration of Interests to the Secretariat

Members of the Committee should inform the Secretariat in writing of their current personal and non-personal interests, when they are appointed, including the principal position(s) held. Only the name of the company and the nature of the interest are required; the amount of any salary etc. need not be disclosed. An

interest is current if the member has an on-going financial involvement with industry, eg if he or she holds shares in industry, has a consultancy contract, or if the member or the department for which he or she is responsible is in the process of carrying out work for industry. Members are asked to inform the Secretariat at any time of any change of their personal interests and will be invited to complete a declaration form once a year. It is sufficient if changes in non-personal interests are reported in the annual declaration form following the change. (Non-personal interests involving less than £1,000 from a particular company in the previous year need not be declared to the Secretariat).

The register of interests should be kept up-to-date and be open to the public.

(ii) Declaration of Interest and Participation at Meetings

Members of the Committee are required to declare any direct interests relating to salaried employment or consultancies, or those of close family members,[1] in matters under discussion at each meeting. Having fully explained the nature of their interest the Chairman will, having consulted the other members present, decide whether and to what extent the member should participate in the discussion and determination of the issue. If it is decided that the member should leave the meeting, the Chairman may first allow them to make a statement on the item under discussion.

Personal liability of Committee members

A Committee member may be personally liable if he or she makes a fraudulent or negligent statement which results in a loss to a third party; or may commit a breach of confidence under common law or a criminal offence under insider dealing legislation, if he or she misuses information gained through their position. However, the Government has indicated that individual members who have acted honestly, reasonably, in good faith and without negligence will not have to meet out of their own personal resources any personal civil liability which is incurred in execution or purported execution of their Committee functions save where the person has acted recklessly. To this effect a formal statement of indemnity has been drawn up.

[1] Close family members include personal partners, parents, children, brothers, sisters and the personal partners of any of these.

Annex 1

THE SEVEN PRINCIPLES OF PUBLIC LIFE

Selflessness
Holders of public office should take decisions solely in terms of the public interest. They should not do so in order to gain financial or other material benefits for themselves, their family, or their friends.

Integrity
Holders of public office should not place themselves under any financial or other obligation to outside individuals or organisations that might influence them in the performance of their official duties.

Objectivity
In carrying out public business, including making public appointments, awarding contracts, or recommending individuals for rewards and benefits, holders of public office should make choices on merit.

Accountability
Holders of public office are accountable for their decisions and actions to the public and must submit themselves to whatever scrutiny is appropriate to their office.

Openness
Holders of public office should be as open as possible about all the decisions and actions that they take. They should give reasons for their decisions and restrict information only when the wider public interest clearly demands.

Honesty
Holders of public office have a duty to declare any private interests relating to their public duties and to take steps to resolve any conflicts arising in a way that protects the public interests.

Leadership
Holders of public office should promote and support these principles by leadership and example.

Annex 2

DIFFERENT TYPES OF INTEREST

The following is intended as a guide to the kinds of interests that should be declared. Where members are uncertain as to whether an interest should be declared they should seek guidance from the Secretariat or, where it may concern a particular product which is to be considered at a meeting, from the Chairman at that meeting. **If members have interests not specified in these notes but which they believe could be regarded as influencing their advice they should declare them.** However, neither the members nor the Secretariat are under any obligation to search out links of which they might *reasonably* not be aware. For example, either through not being aware of all the interests of family members, or of not being aware of links between one company and another.

Personal Interests

A personal interest involves the member personally. The main examples are:

- **Consultancies and/or direct employment** any consultancy, directorship, position in or work for industry which attracts regular or occasional payments in cash or kind;

- **Fee-Paid Work**: any commissioned work by industry for which the member is paid in cash or kind;

- **Shareholdings**: any shareholding or other beneficial interest in shares of industry. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management;

Non-Personal Interests

A non-personal interest involves payment which benefits a department for which a member is responsible, but is not received by the member personally. The main examples are:

- **Fellowships**: the holding of a fellowship endowed by industry;

- **Support by Industry**: any payment, other support or sponsorship which does not convey any pecuniary or material benefit to a member personally, but which does benefit their position or department eg:

i) a grant for the running of a unit or department for which a member is responsible;

ii) a grant or fellowship or other payment to sponsor a post or a member of staff or a post graduate research programme in the unit for which a member is responsible. This does not include financial assistance for students;

iii) the commissioning of research or other work by, or advice from, staff who work in a unit for which the member is responsible.

Members are under no obligation to seek out knowledge of work done for, or on behalf of, the industry or other relevant bodies by departments for which they are responsible, if they would not normally expect to be informed.

- **Trusteeships**: where a member is a trustee of a charity with investments in industry, the Secretariat can agree with the member a general declaration to cover this interest rather than draw up a detailed portfolio.

DEFINITIONS

In this Code, 'the industry' means:

- Companies, partnerships or individuals who are involved with the production, manufacture, sale or supply of products subject to the following legislation;

  The Food Safety Act 1990
  The Medicines Acts 1968 and 1971
  The Food and Environmental Protection Act 1985
  The Consumer Protection Act 1987
  The Cosmetic (Safety) (Amendment) Regulations 1987
  The Notification of New Substances Regulations 1982

- Trade associations representing companies involved with such products;

- Companies, partnerships or individuals who are directly concerned with research, development or marketing of a product which is being considered by the Committees on Toxicity, Mutagenicity, or Carcinogenicity of Chemicals in Food, Consumer Products and the Environment.

In this Code 'the Secretariat' means the Secretariat of the COT/COM/COC.

ANNEX 3

OPENNESS

Introduction

1. The Committee on Toxicity (COT) and its sister committees the Committee on Mutagenicity (COM) and Committee on Carcinogenicity (COC) are non-statutory independent advisory committees who advise the Chief Medical Officer and the Chairman of the Food Standards Agency and, through them, the Government on a wide range of matters concerning chemicals in food, consumer products and the environment.

2. The Government is committed to make the operation of advisory committees such as the COT/COM/COC more open and to increase accountability. Proposals have been published in "Quangos-Opening the Doors" (Cabinet Office, July 1998). The COT/COM/COC have recently considered a number of options for greater openness of Committee business. There was a high level of agreement between the COT/COM/COC regarding the adoption of proposals for greater openness.

3. In discussing these proposals (during the course of 1999) the Committees were aware that the disclosure of information which is of a confidential nature and was communicated in circumstances importing an obligation of confidence is subject to the common law of confidentiality. Guidance is set out in the Code of Practice on Access to Government Information (second edition, 1997). Thus an important aspect of implementing initiatives for greater openness of Committee business concerns setting out clear guidelines for the handling of information submitted on a confidential basis.

General procedures for openness

4. The Committees agreed that the publication of agendas, finalised minutes, agreed conclusions and statements (subject to the adoption of appropriate procedures for handling commercially sensitive information) and appointment of a lay/public interest member to each Committee would help to increase public scrutiny of Committee business. The Committees also agreed that additional open meetings on specific topics where interest groups, consumer organisations etc could attend and participate should be held.

5. A summary of the proposals is tabulated below. A more detailed outline of procedures regarding products where confidential data has been reviewed is given in paragraphs 11-13.

6. The Committees stressed that, in view of the highly technical nature of the discussions, there was a need for all documents released to be finalised and agreed by the Committee, ie any necessary consultation with Members and Chairman should be completed before disclosure.

7. Statements and conclusions should summarise all the relevant data, such as information regarding potential hazards/risks for human health in respect of the use of products and chemicals, and any recommendations for further research.

8. The Committees will be asked for an opinion based on the data available at the time of consideration. It is recognised that, for many chemicals, the toxicological information is incomplete and that recommendations for further research to address these gaps will form part of the Committee's advice.

9. The release of documents (papers, minutes, conclusions and statements) where the COT/COM/COC has agreed an opinion on the available data but where further additional information is required in order to finalise the Committee's conclusions, needs to be considered on a case-by case basis. The relevant considerations include the likelihood that such additional data would alter the Committee's conclusion, any representations made by a company about, for example, commercial harm that early disclosure could cause and also the public interest in disclosure.

10. In the event that the Committees need to consider an item over several meetings, it might be necessary to keep relevant documents (eg papers and minutes) confidential until an agreed opinion (eg statement) is available.

Summary of proposals for committee openness.

Issue	Proposals	Comment
Open meetings on specified topics (eg invited audience, interest groups, consumer organisations, professional societies).	Agreed. Suggestions include meeting at time of release of Annual Report. External consultation on identifying topics for such meetings.	Meetings would be on genetic issues in chemical toxicology, carcinogenicity, mutagenicity and risk assessment. There would be no discussion of individual commercial products.
Agenda	Agreed	Made publicly available via Internet site prior to meeting.
Papers	Agreed	Finalised papers to be made available upon request. Confidential information/ annexes to be removed.
Minutes*	Agreed	Anonymised minutes made available upon request and on Internet site after appropriate consultation with members and agreement by the full committee.
Conclusions/statements*	Agreed	Agreed conclusions/ statements published as appropriate including via the Internet and also made available on request.
Annual Report*	Agreed	Publish in accordance with procedures for previous years.

(* Procedures for handling confidential information outlined in paras 11-13 below)

Procedures for handling confidential information Background

11. COT/COM/COC quite often consider information which has been supplied in confidence. For the most part this comprises information which is commercially sensitive. For example, this could include product formulations/specifications, methods of manufacture, and reports of toxicological investigations and company evaluations and safety assessments.

12. Normal procedure in the past has been to publish a summary of the Committee's advice in the Annual Report and to ask companies to release full copies of submitted reports for retention by the British Library at the completion of a review. Given the clear Ministerial commitment to the

publication of detailed information regarding the activities of advisory committees, and in particular following the assessment of products which are already available to the general public, the COT/COM/COC have begun to adopt where possible a more open style of business where detailed statements have been published via the Internet soon after they have been finalised.

13. Except in cases where there is legislation under which information has been submitted and which deals with disclosure and non-disclosure, the general principle of the common law duty of confidentiality will apply. This means that any information which is of a confidential character and has been obtained in circumstances importing a duty of confidence may not be disclosed unless consent has been given or there is an overriding public interest in disclosure (such as the prevention of harm to others). The following procedure will be adopted which allows confidential information to be identified, assessed and appropriate conclusions/statements to be drafted and published on the basis of a prior mutual understanding with the companies. There is scope for companies to make representations also after submission of the information and prior to publication regarding the commercial sensitivity of data supplied and to comment on the text of statements which are to be published. However, companies would not have a right of veto in respect of such statements.

Procedures prior to committee consideration

Initial discussions

Upon referral to COT/COM/COC the Secretariat will liaise with the relevant company supplying the product in the UK to:

i) Clearly state the policy of Committee openness (as summarised above).

ii) To identify and request the information needed by the COT/COM/COC (eg test reports, publications etc).

Confidential data

iii) The company will be asked to clearly identify any confidential data and the reason for confidentiality.

Handling confidential data

iv) The procedures by which the COT/COM/COC will handle confidential data and the public availability of papers, minutes, conclusions and statements where reference is made to such data will be discussed with the company prior to submission of papers to the Committee(s). The general procedures for handling documents are outlined in paragraphs 4-10 above. Companies will be informed that confidential annexes to Committee papers (eg where detailed information supplied in confidence such as individual patient information and full study reports of toxicological studies) will not be disclosed but that other information will be disclosed unless agreed otherwise with an individual company.

v) The following is a suggested list of information which might be disclosed in COT/COM/COC documents (papers, minutes, conclusions and statements). The list is not exhaustive and is presented as a guide.

a) name of product (or substance/chemical under consideration),
b) information on physico-chemical properties,
c) methods of rendering harmless,
d) a summary of the results and evaluation of the results of tests to establish harmlessness to humans,
e) methods of analysis,
f) first aid and medical treatment to be given in the case of injury to persons.
g) surveillance data (eg monitoring for levels in food, air, or water).

Procedures during and after Committee consideration

vi) The timing of release of Committee documents (papers, minutes, conclusions and statements) where the item of business involved the consideration of confidential data would be subject to the general provisions outlined in paragraphs 4-10 above. Documents would not be released until a Committee - agreed conclusion or statement was available.

vii) The most important outcome of the Committee consideration is likely to be the agreed statement. Companies will be given an opportunity to comment on the statement prior to publication and to make

representations (for example, as to commercial sensitivities in the statement). The Chairman would be asked to consider any comments provided, but companies would not be able to veto the publication of a statement or any part of it. Companies will continue to be asked to release full copies of submitted reports for retention by the British Library at the completion of a review.

ANNEX 4

GLOSSARY OF TERMS

ACUTE	Describes a disease of rapid onset, severe symptoms and brief duration.
ACUTE TOXICITY	Effects that occur over a short period of time (hours or few days) immediately following exposure.
ADDUCT	A chemical grouping which is covalently bound (strong bond formed by the sharing of a pair of electrons) to a large molecule such as DNA (qv) or protein.
Ah RECEPTOR	The Ah (Aromatic hydrocarbon) receptor protein regulates gene expression. The identity of the natural endogenous chemical which bind to the Ah receptor are unknown. A range of chemicals such as chlorinated dibenzodioxins and polychlorinated biphenyls bind to Ah receptor. The available research suggests that binding to the Ah receptor is an integral part of the toxicological mechanism of these compounds.
ALANINE AMINOTRANSFERASE	An enzyme that, when elevated activity is detected in serum, may indicate damage to certain organs.
ALKYLATING AGENTS	Chemicals which leave an alkyl group covalently bound to biologically important molecules such as proteins and DNA (see adduct). Many alkylating agents are mutagenic, carcinogenic and immunosuppressive.
AMES TEST	*In vitro* (qv) assay for bacterial gene mutations (qv) using strains of *Salmonella* typhimurium developed by Ames and his colleagues.
ANEUGENIC	Inducing aneuploidy (qv).
ANEUPLOIDY	The circumstances in which the total number of chromosomes within a cell is not an exact multiple of the normal haploid (see 'polyploidy') number. Chromosomes may be lost or gained during cell division.

ASPARTATE AMINOTRANSFERASE	An enzyme that, when elevated activity is detected in serum, may indicate damage to certain organs.
ASSAY	A procedure for measurement or identification.
B6C3F1 MICE	a particular strain of mice.
BIAS	An inference which at any stage of an epidemiological investigation tends to produce results that depart systemically from the true values (to be distinguished from random error). The term does not necessarily carry an imputation of prejudice or any other subjective factor such as the experimenter's desire for a particular outcome.
ß-ISOMER	Isomers are two or more chemical compounds with the same molecular formula but having different properties owing to a different arrangement of atoms within the molecule. The ß-isomer of alitame is formed when the compound degrades and the atoms within the molecule are rearranged.
BIOAVAILABILITY	A term referring to the proportion of a substance which reaches the systemic circulation unchanged after a particular route of administration.
BIOMARKER	A readily measurable biological concentration or similar quantity which acts as a surrogate for a biological effect.
BRADFORD - HILL CRITERIA	Sir Bradford-Hill established criteria that have been universally used to assist in the interpretation of associations reported from studies:-

STRENGTH – The stronger the association the more likely it is causal. The COC has previously noted that the relative risks of<3 need careful assessment for effects of bias or confounding.

CONSISTENCY – The association has been consistently identified by studies Using different approaches and is also seen in different populations with exposure to the chemical under consideration.

SPECIFICITY – Limitation of the association to specific exposure groups or to specific types of cancers increases likelihood that the association is causal.

TEMPORALITY – The association must demonstrate that exposure leads to cancer. The relationship of time since first exposure, duration of exposure and time since last exposure are all important in assessing casuality.

BIOLOGICAL GRADIENT – If an association reveals a biological gradient or dose-reponse curve, then this evidence is of particular importance in assessing causality.

PLAUSIBILITY – Is there appropriate data to suggest a mechanism by which exposure could lead to concern? However, even if an observed association may be new to science or medicine it should not be dismissed.

COHERENCE – Cause and effect interpretation of data should not seriously conflict with generally known facts.

EXPERIMENT – Can the association be demonstrated. Evidence from experimental animals may assist in some cases. Evidence that removal of the exposure leads to a decrease in risk may be relevant.

ANALOGY – Have other closely related chemicals been associated with cancer.

BRONCHIAL	Relating to the air passages conducting air from the trachea (windpipe) to the lungs.
CARCINOGENICITY BIOASSAY	Tests carried out in laboratory animals, usually rats and mice, to determine whether a substance is carcinogenic. The test material is given, usually in the diet, throughout life to groups of animals, at different dose levels.

CARCINOGENESIS	The origin, causation and development of tumours. The term applies to all forms of tumours, benign as well as malignant (see 'tumour') and not just to carcinomas (qv).
CARCINOGENS	The causal agents which induce tumours. They include external factors (chemicals, physical agents, viruses) and internal factors such as hormones. Chemical carcinogens are structurally diverse and include naturally-occurring substances as well as synthetic compounds. An important distinction can be drawn between *genotoxic* (qv) carcinogens which have been shown to react directly with and mutate DNA, and *non-genotoxic* carcinogens which act through other mechanisms. The activity of genotoxic carcinogens can often be predicted from their chemical structure - either of the parent compound or of activated metabolites (qv). Most chemical carcinogens exert their effects after prolonged exposure, show a dose-response relationship and tend to act on a limited range of susceptible target tissues. Carcinogens are sometimes species- or sex-specific and the term should be qualified by the appropriate descriptive adjectives to aid clarity. Several different chemical and other carcinogens may interact, and constitutional factors (genetic susceptibility, hormonal status) may also contribute, emphasising the multifactorial nature of the carcinogenic process.
CARCINOMA	Malignant tumour arising from epithelial cells lining, for example, the alimentary, respiratory and urogenital tracts and from epidermis, also from solid viscera such as the liver, pancreas, kidneys and some endocrine glands. (See also 'tumour').
CASE-CONTROL STUDY	(Synonyms - case comparison study, case referent study). A study that starts with the identification of persons with the disease of interest and a suitable control group of persons without the disease. The relationship of some attribute to the disease (such as occupational exposure to a carcinogen) is examined by comparing the disease and nondiseased with regard to how frequently the attribute is implicated in each of the groups.

CELLS IN CULTURE	Cells which have been isolated from animals and grown in the laboratory.
CELL TRANSFORMATION ASSAY	See Transformation.
CENTRILOBULAR HEPATOCYTE VACUOLISATION	Vacuolation of cells surrounding the central vein in a liver lobule.
CHROMOSOME ABERRATION	Collective term of particular types of chromosome damage induced after exposure to exogenous chemical or physical agents which damage the DNA. (see clastogen).
CHRONIC	Describing a disease of long duration involving very slow changes. Such disease is often of gradual onset. The term does not imply anything about the severity of the disease.
CLASTOGEN	An agent that produces chromosome breaks and other structural aberrations such as translocations (qv). Clastogens may be viruses or physical agents as well as chemicals. Clastogenic events play an important part in the development of some tumours.
COHORT	A defined population.
COHORT STUDY	(Synonyms - follow-up, longitudinal, prospective study) The method of epidemiological study in which subsets of a defined population can be identified who may be exposed to a factor or factors hypothesized to influence the probability of occurrence of a given disease. An essential feature of the method is observation of the population for a sufficient number of person-years to generate reliable incidence or mortality rates in the population subsets. This generally implies study of a large population and/or study for a prolonged period of time.
CONGENER	Compounds varying in chemical structure but with similar biological properties.

COVALENT	The type of binding formed by the sharing of an electron pair between two atoms. Molecules are combinations of atoms bound together by covalent bonds.
CYTOCHROME	Haem proteins that catalyse electron transfer reactions. Cytochrome P450 is a collective term for an extensive family of haem proteins involved in enzymic oxidation of a wide range of substances and their conversion to forms that are more easily excreted. In some cases the metabolites produced may be reactive and may have carcinogenic potential.
CYTOGENETIC	Concerning chromosomes, their origin, structure and function.
DELETION	Usually a chromosome aberration in which a proportion of a chromosome is lost.
DIETARY REFERENCE VALUE (DRV)	A term used to cover LRNI (qv), RNI (qv) and safe intake.
DNA (DEOXYRIBONUCLEIC ACID)	The carrier of genetic information for all living organisms except the group of RNA viruses. Each of the 46 chromosomes in normal human cells consists of 2 strands of DNA containing up to 100,000 nucleotides, specific sequences of which make up genes (qv). DNA itself is composed of two interwound chains of linked nucleotides, each nucleotide consisting of 3 elements: a pentose sugar, a phosphate group and a nitrogenous base derived from either purine (adenine, guanine) or pyrimidine (cytosine, thymine).
DOMINANT LETHAL ASSAY	See Dominant Lethal mutation.
DOMINANT LETHAL MUTATION	A dominant mutation that causes death of an early embryo.
ENDOMETRIAL	Relating to the lining of the uterus.

ENDOMETRIOSIS	A condition in which the tissue lining the womb (endometrium) is present at other sites in the body. The tissue undergoes the periodic changes similar to the endometrium and causes pelvic pain and painful periods.
EPIDEMIOLOGY	Study of the distribution and, in some instances, the causal factors of disease in communities and populations.
EPITHELIUM	The tissue covering the outer surface of the body, the mucous membranes and cavities of the body.
ERYTHEMA	Reddening of the skin due to congestion of blood.
ERYTHROCYTE	Red blood cell.
EXOGENOUS	Arising outside the body.
FLUORESCENCE IN-SITU HYBRIDISATION	A technique which allows individual chromosomes and their centromeres (qv) to be visualised in cells.
FOETOTOXIC	Causing toxic, potentially lethal effects to the developing foetus.
FIBROSARCOMA	A malignant tumour arising from connective tissue (see 'tumour').
FORESTOMACH	(See glandular stomach).
GAVAGE	Administration of a liquid via a stomach tube, commonly used as a dosing method in toxicity studies.
GENE	The functional unit of inheritance: a specific sequence of nucleotides along the DNA molecule, forming part of a chromosome.
GENETICALLY MODIFIED ORGANISM	An organism which has had genetic material from another species inserted into its cells.
GENOTOXIC	The ability of a substance to cause DNA damage, either directly or after metabolic activation (see also 'carcinogens').

GLANDULAR STOMACH	The stomach in rodents consists of two separate regions - the fore stomach and the glandular stomach. The glandular stomach is the only area directly comparable to human situations.
HEPATIC	Pertaining to the liver
HEPATOCYTE	The principal cell type in the liver, possessing many metabolizing enzymes (see 'metabolic activation').
HEPATOTOXIC	Causing damage to the liver.
HYPERPLASIA	An increase in the size of organs and tissues due to an increase in the total numbers of the normal cell constituents.
HYPERTROPHY	An increase in the size of cells or tissues.
INTRAPERITONEAL	Within the abdominal cavity.
IN VITRO	A Latin term used to describe effects in biological material outside the living animal.
IN VIVO	A Latin term used to describe effects in living animals.
IPCS	The World Health Organization's International Programme on Chemical Safety.
ISOMERS	See ß-isomer.
LD50	The dose of a toxic compound that causes death in 50% of a group of experimental animals to which it is administered. It can be used to assess the acute toxicity of a compound.
LEUKAEMIA	A group of neoplastic disorders (see 'tumour') affecting blood-forming elements in the bone marrow, characterised by uncontrolled proliferation and disordered differentiation (qv) or maturation (stage which forms final cell types). Examples include the lymphocytic leukaemias which develop from lymphoid (qv) cells and the myeloid leukaemias which are derived from myeloid cells (producing red blood cells, mainly in bone marrow).

LEYDIG CELL ADENOMA	Benign tumour (qv) of the cells interspersed between the seminiferous tubules of the testis.
LIGAND	A molecule which binds to a receptor.
LIPIDS	Fats, substances containing a fatty acid and soluble in alcohols or ether, but insoluble in water.
LIPOPHILIC	'Lipid liking' - a substance which has a tendency to partition into fatty materials.
LYMPHOCYTE	Type of white blood cell.
LYMPHOMA	Malignant tumours arising from lymphoid tissues. They are usually multifocal, involving lymph nodes, spleen, thymus and sometimes bone marrow and other sites outside the anatomically defined lymphoid system. (See also 'tumour').
MALIGNANCY	See 'tumour'.
META-ANALYSIS	A statistical procedure to summarise quantitative data from several different epidemiological studies. It is most commonly used in summarising epidemiological evidence with respect to disease incidence.
METABOLIC ACTIVATION	Conversion by enzymes of a chemical from one state to another, for example by chemical reactions such as hydroxylation, epoxidation or conjugation. The term is used in a more narrow sense to describe the addition of a mammalian cell free preparation from livers of rats pre-treated with a substance which stimulates production of metabolising enzymes. These preparations are added to *in vitro* short-term tests to mimic the metabolic activation typical of mammals.
METABOLISM	Changes made to a compound by biological systems to modify it's properties.
METABOLITE	Product formed from the original compound by enzymic reactions in the body/cell.

METAPHASE	Stage of cell division (mitosis and meiosis) during which the chromosomes are arranged on the equator of the nuclear spindle (the collection of microtubule filaments which are responsible for the movement of chromosomes during cell division). As the chromosomes are most easily examined in metaphase, cells are arrested at this stage for microscopical examination for chromosome aberrations (qv) - known as metaphase analysis.
METASTASIS	The process whereby malignant cells become detached from the primary tumour mass, disseminate (mainly in the blood stream or in lymph vessels) and 'seed out' in distant sites where they form secondary or metastatic tumours. Such tumours tend to develop at specific sites and their anatomical distribution is often characteristic; it is non-random. The capacity to metastasise is the single most important feature of malignant tumours (see tumour).
MICRONUCLEI	Isolated or broken chromosome fragments which are not expelled when the nucleus is lost during cell division, but remain in the body of the cell forming micronuclei. Centromere positive micronuclei contain DNA and/or protein material derived from the centromere (qv). The presence of centromere positive micronuclei following exposure to chemicals can be used to evaluate the aneugenic (qv) potential of chemicals.
MICRONUCLEUS TEST	See Micronuclei.
MITOSIS	The type of cell division which occurs in somatic cells when they proliferate. Each daughter cell has the same complement as the parent cell.

MOUSE LYMPHOMA ASSAY	An *in vitro* assay for gene mutation in mammalian cells using a mouse lymphoma cell line L5178Y, which is heterozygous for the gene (carries only one functional gene rather than a pair) for the enzyme thymidine kinase ($TK^{+/-}$). Mutation of that single gene is measured by resistance to toxic trifluorothymidine. Mutant cells produce two forms of colony - large, which represent mutations within the gene and small, which represent large genetic changes in the chromosome such as chromosome aberrations. Thus this assay can provide additional information about the type of mutation which has occurred if colony size is scored.
MOUSE SPOT TEST	An *in vivo* test for mutation, in which pregnant mice are dosed with the test compound and mutations are detected by changes (spots) in coat colour of the offspring. Mutations in the melanocytes (skin pigment cells) of the developing fetus are measured.
MRC	Medical Research Council.
MUCOSAL	Regarding the mucosa or mucous membranes, consisting of epithelium (qv) containing glands secreting mucus, with underlying layers of connective tissue and muscle.
MUTATION	A permanent change in the amount or structure of the genetic material in an organism which can result in a change in the characteristics of the organism. The alternation may involve a single gene, a block of genes, or a whole chromosome. Mutations involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Changes involving whole chromosomes may be numerical or structural. A mutation in the germ cells of sexually reproducing organisms may be transmitted to the offspring, whereas a mutation that occurs in somatic cells may be transferred only to descendent daughter cells.
MYCOTOXIN	Toxic compound produced by a fungus.
NEOPLASM	See ‘tumour’.

NEOPLASTIC	Abnormal cells, the growth of which is more rapid that that of other cells.
NEUROBEHAVIOURAL	Of behaviour determined by the nervous system.
NEUROTOXICITY	Toxicity to the nervous system.
NOAEL	No Observed Adverse Effect Level, the highest administered dose at which no toxic effect has been observed.
NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL)	The highest administered dose at which no toxic effect has been observed.
NON-GENOTOXIC	See 'carcinogens'.
ODDS RATIO (OR)	A measure of association which is interpreted similarly to the Relative Risk (see Relative Risk); it is similar in magnitude to the Relative Risk in the case of rare diseases.
OECD	Organization for Economic Cooperation and Development.
OEDEMA	Excessive accumulation of fluid in body tissues.
OESTROGEN	Is the hormone which develops and maintain female bodily characteristics.
OESTROGEN ACTIVITY	Hormonal activity of the female steroid hormone oestrogen or its analogues.
ORGANOCHLORINE	A group of chemical compounds used as pesticides.
^{32}P POSTLABELLING	A sensitive experimental quantitatively method designed to measure low levels of DNA adducts induced by chemical treatment.
PHYTOESTROGEN	Phytoestrogens are plant chemicals that similar to the human female hormone oestrogen but are much less potent (10,000 -140,000 times less potent in animal models).

PLASTICISER	A substance which increases the flexibility of certain plastics.
POLYMER	A very large molecule comprising a chain of many similar or identical molecular sub units (monomers) joined together (polymerized). An example is the polymer glycogen, formed from linked molecules of the monomer glucose.
PREVALENCE	The number of cases of a disease that are present in a population at one point in time.
RECEPTOR	A small, discrete area on the cell membrane or within the cell with which specific molecules interact to initiate a change in the working of a cell.
REFERENCE NUTRIENT INTAKE (RNI)	An amount of the nutrient that is enough, or more than enough, for most (usually at least 97%) of people in a group. If the average intake of a group is at the RNI, then the risk of deficiency in the group is very small.
RELATIVE RISK	A measure of the association between exposure and outcome. The rate of disease in the exposed population divided by the rate of disease among the unexposed population in a cohort study. A RR of 2 means that the exposed group has twice the disease risk compared to the unexposed group.
RENAL	Relating to the kidney.
SCF	The European Commission's Scientific Committee on Food.
SERUM	The fluid remaining after blood has clotted.
SISTER CHROMATID EXCHANGE (SCE)	Exchange of genetic material between two sub-units of a replicated chromosome.
TDI	See 'Tolerable Daily Intake'.
TERATOGEN	A substance which, when administered to a pregnant woman or animal, can cause congenital abnormalities (deformities) in the baby or offspring.

TERATOGENIC RISK	Risk that a compound will cause developmental abnormalities in the foetus.
THRESHOLD	The lowest dose which will produce a toxic effect and below which no toxicity is observed.
TOLERABLE DAILY INTAKE (TDI)	An estimate of the amount of contaminant, expressed on a body weight basis, that can be infested daily over a lifetime without appreciable health risks.
TOXIC EQUIVALENCY FACTOR (TEF)	A measure of relative toxicological potency of a chemical compared to a well characterised reference compound. TEFs can be used to sum the toxicological potency of a mixture of chemicals which are all members of the same chemical class, having common structural, toxicological and biochemical properties. Systems have been published for chlorinated dibenzodioxins and dibenzofurans and for polycylic aromatic hydrocarbons.
TOXICOKINETICS	The description of the fate of chemicals in the body, including a mathematical account of their absorption, distribution, metabolism and excretion.
TRANSFORMATION	The process by which a normal cell acquires the capacity for neoplastic growth. Complete transformation occurs in several stages both *in vitro* and *in vivo*. One step which has been identified *in vitro* is 'immortalisation' by which a cell acquires the ability to divide indefinitely in culture. Such cells do not have the capacity to form tumours in animals, but can be induced to do so by extended passage *in vitro*, by treatment with chemicals, or by transfection with oncogene DNA. The transformed phenotype so generated is usually, but not always, associated with the ability of the cells to grow in soft agar and to form tumours when transplanted into animals. It should be noted that each of these stages of transformation can involve multiple events which may or may not be genetic. The order in which these events take place, if they occur at all, *in vivo* is not known.
TRANSGENIC	Genetically modified to contain genetic material from another species (see also genetically modified organism).

TRANSGENIC ANIMAL MODELS	Animals which have extra (exogenous) fragments of DNA incorporated into their genomes. This may include reporter genes to assess *in-vivo* effects such as mutagenicity in transgenic mice containing a recoverable bacterial gene (lacZ or *lac I*). Other transgenic animals may have alterations of specific genes believed to be involved in disease processes (eg cancer). For example strains of mice have been bred which carry an inactivated copy of the p53 tumour suppressor gene (qv) -, or an activated form of the *ras* oncogene which may enhance their susceptibility of the mice to certain types of carcinogenic chemicals.
TUMOUR	(Synonym - neoplasm) A mass of abnormal, disorganised cells, arising from pre-existing tissue, which are characterised by excessive and uncoordinated proliferation and by abnormal differentiation (qv). BENIGN tumours show a close morphological resemblance to their tissue of origin; grow in a slow expansile fashion; and form circumscribed and (usually) encapsulated masses. They may stop growing and they may regress. Benign tumours do not infiltrate through local tissues and they do not metastasise (qv). They are rarely fatal. MALIGNANT tumours (synonym - cancer) resemble their parent tissues less closely and are composed of increasingly abnormal cells in terms of their form and function. Well differentiated examples still retain recognizable features of their tissue of origin but these characteristics are progressively lost in moderately and poorly differentiated malignancies: undifferentiated or anaplastic tumours are composed of cells which resemble no known normal tissue. Most malignant tumours grow rapidly, spread progressively through adjacent tissues and metastasise to distant sites. Tumours are conventionally classified according to the anatomical site of the primary tumour and its microscopical appearance, rather than by cause. Some common examples of nomenclature are as follows:- Tumours arising from epithelia (qv): *benign* - adenomas, papillomas*; malignant* - adenocarcinomas, papillary carcinomas.

	Tumours arising from connective tissues such as fat, cartilage or bone: *benign* - lipomas, chondromas, osteomas; *malignant* - fibrosarcomas, liposarcomas, chondrosarcomas, osteosarcomas. Tumours arising from lymphoid tissues are malignant and are called lymphomas (qv); they are often multifocal. Malignant proliferations of bone marrow cells are called leukaemias. Benign tumours may evolve to the corresponding malignant tumours; examples involve the adenoma -> carcinoma sequence in the large bowel in humans, and the papilloma -> carcinoma sequence in mouse skin.
UNSCHEDULED DNA SYNTHESIS (UDS)	DNA synthesis that occurs at some stage in the cell cycle other than the S period (the normal or 'scheduled' DNA synthesis period) in response to DNA damage. It is usually associated with DNA repair.
WHO-IPCS/ECEH	The World Health Organization's European Centre for Environment and Health and the WHO's International Programme on Chemical Safety.
XENOBIOTIC	A chemical foreign to the biologic system.
XENOESTROGEN	A 'foreign' compound, ie not natural to the body, with oestrogenic activity.

ANNEX 5

Index to subjects and substances considered in previous Annual Reports of the Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

ANNEX 6

Publications produced by the Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

1991 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321529 0 Price £9.50.

1992 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321604-1 Price £11.70.

1993 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321808-7 Price £11.95.

1994 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321912-1 Price £12.50.

1995 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321988-1 Price £18.50.

1996 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. The Stationery Office ISBN 0 11 322115-0 Price £19.50.

1997 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Department of Health.

1998 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Department of Health.

1999 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Department of Health.

Guidelines for the Testing of Chemicals for Toxicity DHSS Report on Health and Social Subjects 27 HMSO ISBN 0 11 320815 4 Price £4.30.

Guidelines for the Evaluation of Chemicals for Carcinogenicity DH Report on Health and Social Subjects 42 HMSO ISBN 0 11 321453 7 Price £7.30.

Guidelines for the Testing of Chemicals for Mutagenicity DH Report on Health and Social Subjects 35 HMSO ISBN 0 11 321222 4 Price £6.80.

Guidelines for the Preparation of Summaries of Data on Chemicals in Food, Consumer Products and the Environment submitted to DHSS Report on Health and Social Subjects 30 HMSO ISBN 0 11 321063 9 Price £2.70.

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Peanut Allergy, Department of Health (1998).

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Organophosphates, Department of Health (1998).

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: Adverse Reactions to Food and Food Ingredients, Food Standards Agency (2000).

COM Guidance on a Strategy for Testing of Chemicals for Mutagenicity, Department of Health (2000).

If you require any further information about the work of the committees or the contents of this report please contact:

Keith Butler
Administrative Secretary COT
Food Standards Agency
Room 511C
Aviation House
125 Kingsway
London WC2B 6NH

Tel: +44 (0)20 7276 8522
Fax:+44 (0)20 7276 8513
Email: Keith .Butler@foodstandards.gsi.gov.uk
Website:http://www.foodstandards.gov.uk/committees/cot

Khandu Mistry
Administrative Secretary COM/COC
Department of Health
Room 692D
Skipton House
80 London Road
LONDON SE1 6LH

Tel: +44 (0)20 7972 5020
Fax:+44 (0)20 7972 5156
Email: Khandu.Mistry@doh.gsi.gov.uk
Website: http://www.doh.gov.uk/com.htm
Website: http://www.doh.gov.uk/coc.htm

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