The Interdepartmental Group
on Health Risks from Chemicals

Assessment of chemical carcinogens:

Background to general principles

of a weight of evidence approach

cr8

The Interdepartmental Group on Health Risks from Chemicals aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals.

The Group contributes to the work of the Interdepartmental Liaison Group on Risk Assessment as outlined in its second report to Ministers in 1998, '*Risk Assessment and Risk Management: Improving Policy and Practice within Government Departments*'.

The Steering Committee of the Interdepartmental Group on Health Risks from Chemicals comprises participants from the Department for Environment, Food and Rural Affairs, the Department of Health, the Department of Trade and Industry, the Home Office, the Environment Agency, the Health and Safety Executive, the Food Standards Agency, the Medicines Control Agency, the Pesticides Safety Directorate, the Veterinary Medicines Directorate, the Biotechnology and Biological Sciences Research Council, the Medical Research Council, the Natural Environment Research Council and the Institute for Environment and Health.

The Secretariat is based at the MRC Institute for Environment and Health.

The Interdepartmental Group on Health Risks from Chemicals operates as a subgroup of the Interdepartmental Liaison Group on Risk Assessment.

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Contents

1 GENERAL INTRODUCTION 3

1.1 Aim of the report 3

1.2 Background 3

1.3 Data collection and presentation 4

2 METHODS USED TO IDENTIFY POTENTIAL CHEMICAL CARCINOGENS 5

2.1 Introduction 5

2.2 Epidemiology 5

2.3 Mutagenicity 6

2.4 Carcinogenicity studies 7

2.5 Mechanisms of action 8

3 RISK ASSESSMENT 9

3.1 Genotoxic carcinogens 9

3.2 Non-genotoxic carcinogens 9

REFERENCES 11

ANNEX Glossary 13

MEMBERS OF THE IGHRC STEERING COMMITTEE 15

MEMBERS OF THE IGHRC EXECUTIVE COMMITTEE 16

1 General introduction

1.1 Aim of the report

The aim of this document is to summarise, in one place, the available information on a weight of evidence approach as used in the UK for the hazard assessment of chemical carcinogens; currently such information is spread over several UK Government documents (DH, 1989, 1991, 2000). This report is intended for people not familiar with current guidance and for officials in policy involved in risk assessment. Thus it is hoped that compiling the relevant information in one document will be of benefit to those involved in the risk assessment of chemical carcinogens in the UK.

1.2 Background

Chemicals and chemical technologies are essential to most manufacturing and many service operations, and to the general population in daily life. However, in some circumstances chemicals may have the potential to cause harm to human health, and assessments have to be carried out to ensure that risks from the production, use and disposal of chemicals are properly managed. In the UK chemical risk assessments are routinely conducted by government departments and agencies (Risk Assessment and Toxicology Steering Committee, 1999a,b). Recent UK Government reports (DETR, 1999; HSE, 1999) re-inforce the Government's commitment to prevent harm to the environment and people's health from exposure to chemicals.

A variety of evidence should be considered when evaluating the carcinogenic hazard of a chemical to human health. This includes evidence from carcinogenicity bioassays in animals and from structure activity relationship data, and *in vitro* and *in vivo* data from mechanistic studies (in particular, mutagenicity). Also there may be epidemiology data that provide direct evidence for carcinogenic effects in humans for chemicals that have been in use for about 10 years or more (to allow for the long latent period between exposure and the development of cancer). Consideration is given to whether the overall weight of evidence supports (or does not support) the hypothesis that the agent of concern presents a carcinogenic hazard to humans. In practice weighing this evidence includes the evaluation of individual studies, combining and assessing the significance of results of the various 'groups' of studies (e.g. to measure mutagenicity), and making an overall evaluation of the hazard to humans; expert judgement is required at all stages. Clearly when using these data to identify risks that may be associated with this hazard, sound information on exposure levels are critical.

The process of risk assessment is subject to a number of limitations and uncertainties (Risk Assessment and Toxicology Steering Committee, 1999b). For the vast majority of chemicals, assessment of risk relies on data from either experiments on animals or *in vitro* studies, owing to the difficulties and ethical considerations in obtaining human data. Uncertainties lie in the extrapolation of experimental data to the human situation, in the potential variations in susceptibility between individuals and in estimates of exposure to chemicals. The methods used to deal with the uncertainties inherent in the process of risk assessment may vary depending on the use of the chemical or the exposure scenario (such as route, level, exposed population; Risk Assessment and Toxicology Steering Committee, 1999b). Although the reasons for the use of different approaches may be justifiable, they may not always be made clear. The development of techniques to help reduce uncertainties in the risk assessment process will result in increased confidence in the process and in the risk management choices that flow from risk assessments.

This report by the Interdepartmental Group on Health Risks from Chemicals (IGHRC) has been prepared in accordance with commitments made in the *'First report and Forward plan to 2002'* (IGHRC, 2000) to produce a document on the use, in the UK, of a weight of evidence approach to assessing chemical carcinogens. The forward plan was, itself, a response to recommendations made by the Risk Assessment and Toxicology Steering Committee (the forerunner of the IGHRC) to facilitate the coordination across UK Government departments and agencies of efforts to use recent scientific advances to improve risk assessment (Risk Assessment and Toxicology Steering Committee, 1999b,c,e,f).

1.3 Data collection and presentation

The UK documents pertaining to the weight of evidence approach for evaluating carcinogens have been produced by the Department of Health (DH) through their Expert Committees and the bulk of this document is based on the guidance documents produced by these committees. Methods used to identify potential chemical carcinogens are outlined in Section 2, and the assessment of risks from chemical carcinogens is described in Section 3. Material in Sections 2 and 3 is largely taken from the guidance documents produced by the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) and its sister Committee on Mutagenicity (COM). In addition, the results from the International Programme on Chemical Safety (IPCS) harmonisation project (relating to mutagenicity and carcinogenicity) are considered. A glossary of terms is presented at the end of the document.

2 Methods used to identify potential chemical carcinogens

2.1 Introduction

The evidence that a chemical poses a carcinogenic hazard to humans may be obtained from several sources. It is important that all the relevant data are considered, including background information on the toxicological and metabolic profile of the chemical. Expert judgement is then applied to the data in order to draw conclusions as to whether a chemical should be regarded as a human (or potential human) carcinogen.

2.2 Epidemiology

Sound epidemiological evidence for carcinogenicity is very useful, when available, because the data are derived directly from human populations, and the problem of extrapolating from observations in experimental animals is avoided. A number of different types of studies are available and are outlined below.

Limited information on carcinogenicity can be derived from ecological studies (sometimes called correlation studies), which involve investigation of populations such as those in a particular geographic area or time period. Information is rarely available on exposure at the individual level, or on confounding factors and these studies are only of value in generating hypotheses.

More definitive information can be obtained from analytical studies, which consider risk to the individual. There are two types of analytical study, case–control and cohort. In the case–control studies a comparison is made between people with the cancer and a suitable control group. Such studies are particularly valuable in testing hypotheses generated from case reports or from ecological studies. Cohort studies are the basic tool of cancer epidemiology and, with their various adaptations, are the preferred means of investigation where feasible. In prospective cohort studies a group (or cohort) of individuals, for whom information is available on the exposure of interest and other covariants (such as smoking), is followed forward in time and the development of cancer is documented. More frequently attempts are made to use existing records of past exposures to define a group, or cohort, which is then traced forward in time to the present, noting those individuals who have developed cancer, often determined from mortality data. These are called historic or retrospective cohort studies.

Well-designed epidemiology studies are difficult to perform and are time-consuming. Account must be taken of bias, confounding and measurement errors. An added complication for the evaluation of chemical carcinogenesis is that there is a long latent period between initial exposure and the development of tumours (in range 10–40 years). For most chemicals such long-term data on associations between exposure and cancer in humans are not available.

When epidemiological studies are available, results are valuable provided that careful consideration is given to key factors in the interpretation of such studies. The COC guidelines (summarised in Box 1) note the need to give attention to several aspects, which illustrate the complexity of such studies, and the need for expert judgement when interpreting the results (DH, 1991).

For most chemicals, sound epidemiological data will not be available. Information to assess the carcinogenic potential of a compound will, in the main, be based on data on the mutagenicity or genotoxicity of a chemical and the results from carcinogenicity bioassays.

Box 1 COC guidelines for the interpretation of epidemiological studies

- The study population, disease (or diseases) and exposure should be well defined. Cases in the study population should have been identified in a way that was independent of the exposure of interest, and exposure assessed in a way that was not related to disease status.
- Account should be taken in the study design and analysis of other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may be more appropriate than those with national rates. Internal comparisons of disease frequency among individuals at different levels of exposure should also have been made in the study.
- Information should be available on the accuracy of the estimation of exposure and confounding variables and a sensitivity analysis performed to indicate the extent to which inaccuracies of measurement have affected the estimates of effect.
- The authors should report the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should quote the numbers of exposed and unexposed cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should be given to avoid the possibility of reporting bias. In a case–control study the effects of investigated factors other than the exposure of interest should be reported, as well as some rough indication of the number of comparisons made.
- The statistical methods used to obtain estimates of relevant risk, absolute cancer rates, confidence intervals and significance tests and to adjust for confounding should be clearly stated by the authors.

2.3 Mutagenicity

A common mechanistic pathway, relating to the induction of mutations in somatic cells, has been demonstrated for many, but not all, chemical carcinogens. A mutation is a permanent change in the amount or structure of the genetic material in an organism that can result in a change in the phenotype of the organism. Unlike a mutation in the germ cells, which can be transmitted to the offspring, a mutation that occurs in somatic cells can only be transferred to descendent daughter cells; however, this may lead to a clone of transformed cells and ultimately a malignant tumour.

A wide spectrum of mutational changes has been implicated in the induction of neoplasms and the link between mutation and cancer is well recognised. It is prudent to assume that any chemical that is capable of causing mutation *in vivo* in mammals is a potential human carcinogen.

Thus screening for mutagenicity provides crucial information on the potential carcinogenicity of a compound, and on the mechanisms involved.

Approaches to screening for mutagenicity, and the implications for carcinogenicity are considered in detail in the COM and COC guidelines (DH, 1989, 1991). The COM have recently revised guidance (DH, 2000) on a strategy for testing but this is based on similar general principles to those outlined in the strategy of testing chapter in the 1989 guidelines*.

In order to obtain definitive information on the mutagenic potential of a chemical, data on three levels of mutation (gene, structural chromosome damage and numerical chromosome damage) are necessary. Adequate screening data for mutagenic potential can be obtained using three *in vitro* studies (bacterial assay for gene mutation, *in vitro* metaphase analysis in mammalian cells and another mammalian cell assay such as the mouse lymphoma assay). If performed to the current recommended protocols these three types of test will detect virtually all compounds with mutagenic activity.

If such activity is demonstrated clearly in any one of these *in vitro* tests, data are needed from *in vivo*

* The revised COM strategy of testing is based on a similar process. The emphasis in stage one is on initial screening using three *in vitro* tests. The only difference here is that there is a recommendation to look for indicators for aneugenicity in the *in vitro* cytogenetic assay (or the *in vitro* micronucleus test if this is used as an alternative). As in the earlier guidelines, stage two relates to *in vivo* testing in somatic cells (a wider range of methods are considered) and stage three involves *in vivo* germ cell assays.

studies to investigate whether the mutagenic potential can be expressed *in vivo*, for example in a mouse bone marrow assay for clastogenicity. Such data are important before any definite conclusions can be drawn about hazard, since it is possible that some compounds are mutagenic only *in vitro* and do not express such activity *in vivo* (e.g. due to rapid detoxification and failure to reach DNA, lack of absorption etc).

The testing strategy recommended by the COM, to investigate a compound's inherent mutagenic potential (based on *in vitro* studies) and, if this is positive, to proceed to investigate whether such activity is expressed *in vivo*, provides important information on the carcinogenic potential of a substance. There is now general agreement (both internationally, e.g. the International Agency for Research in Cancer (IARC)[1], and in the UK) that chemicals with clear mutagenic activity *in vivo* should be regarded as potential carcinogens.

Furthermore, the use of a mutagenicity strategy along the lines recommended by the COM for predicting human carcinogenic/mutagenic hazard has also been recommended by the International Programme in Chemical Safety (IPCS[2]; Ashby, *et al.*, 1996).

There is thus a wide international consensus on this approach.

Mutagenicity data may, therefore, be of key importance in deciding whether a chemical should be regarded as a potential genotoxic carcinogen (in some cases this will be the only information available, and judgement will be needed as to whether this is adequate for the specific situation). However, mutagenicity data provide no information on carcinogenic potency or on target tissues.

A pragmatic approach is taken as to whether a compound is not genotoxic. In most cases negative results in the three recommended *in vitro* studies, in the absence of any structural alerts for DNA reactivity of the compound or its metabolites, will be considered to indicate that the compound has no genotoxic activity. In some cases judgement will have to be made as to whether two negative tests provide adequate data for lack of an effect.

[1] As noted in the Preamble to its Monographs on the Evaluation of Carcinogenic Risks to Humans

[2] The IPCS is a joint World Health Organization/International Labour Organisation/United Nations Environment Programme venture

However, mutagenicity tests will provide no information on non-genotoxic carcinogens. There are a number of chemicals that, although carcinogenic in animals, show no detectable mutagenic activity despite intensive testing. Such compounds are described as non-genotoxic carcinogens. There are many possible mechanisms to account for such effects (see below) and, unlike mutagenicity testing for genotoxic carcinogens, there are no recognised short-term tests that can be used to detect such chemicals. Currently, the only approach to identifying non-genotoxic carcinogens is to carry out long-term studies in animals to assess the ability of the compound to induce tumours.

2.4 Carcinogenicity studies

The basic features of carcinogenicity testing in animals are well established. These are described in the relevant OECD guidelines (OECD, 1981a,b). Since cancer induction by chemicals generally requires prolonged administration, with an increased incidence of tumours often only being seen near the end of the life span, it is essential that dosing be carried out for a major proportion of the life span (at least 1½ years for mice and 2 years for rats). Also, sufficient numbers of animals are needed (at least 50 per sex per dose level) to enable detection of increases of the order of 5% or more above the spontaneous incidence of most tumours that arise in ageing animal populations.

In outline, the carcinogenicity bioassay is based on a comparison of the incidence, nature and time of occurrence of neoplasms in treated animals and controls. The conclusion that a substance has a carcinogenic effect depends on showing that the test substance has materially increased the incidence of neoplasms, made them appear earlier in life, or produced unusual types of cancers in treated animals, all in comparison with the spontaneous tumours found in the control groups. Knowledge of the historic tumour incidence for the specific strain of animal in question is important.

Adequate concurrent controls are essential to be able to interpret the significance of the effects seen in the light of the somewhat variable background incidences of spontaneous tumours and other lesions that are seen in any population of ageing animals. Expert judgement is needed.

The COC guidelines consider a number of critical issues and common problems in the design of carcinogenicity bioassays. These are still pertinent.

2.5 Mechanisms of action

As described above, carcinogenic chemicals are considered to fall into two general classes — those that are genotoxic (i.e. the compound, or its metabolites, reacts with DNA) and those that are non-genotoxic.

As noted earlier, genotoxic compounds are readily identified by appropriate, adequately conducted screening tests for mutagenicity. Initial screening is carried out *in vitro* followed by investigations to determine whether this activity can be expressed *in vivo*. In contrast to non-gentoxic carcinogens (see below), genotoxic carcinogens usually have a range of target tissues and show activity across species, including humans. Chemicals that have clear mutagenic activity *in vivo* are regarded as potential carcinogens. There are no clear genotoxic animal carcinogens for which the effects are believed to be irrelevant to humans.

Non-genotoxic carcinogens exert their carcinogenic effects through processes that do not involve direct binding of the chemical or its metabolites with DNA. The biochemical modes of action are diverse. Examples include sustained cytotoxicity and cell proliferation, cytochrome P-450 enzyme induction, peroxisome proliferation, α2u microglobulin binding and hormonal effects (chronic perturbation of the endocrine system etc.). In the case of non-genotoxic carcinogens it is very important to give careful consideration to the mode of action. This is both to enable an assessment of relevance to humans and to enable the 'no effect level' for a key precursor event to be identified. The latter is important in risk assessment (see Section 3). Non-genotoxic carcinogens are usually species and tissue specific and, in a number of cases, it is now generally accepted that the mode of action in experimental animals is not relevant to induction of cancer in humans (e.g. the male rat kidney specific neoplasia induced by compounds that bind to rat α2u microglobulin (such as *d*-limonene)). Thus just because a non-genotoxic chemical causes an increase in a particular cancer in animals it cannot be automatically concluded that it is a potential human carcinogen. Expert judgement is needed to interpret the results of the animal bioassay. The tissue sites where tumours are induced are frequently those where there is a significant incidence of spontaneous tumours.

IPCS (Sonich-Mullin *et al*., 2001) have recently developed a conceptual framework that provides a generic approach to the principles commonly used for evaluating a postulated mode of action for tumour induction in animals by a chemical carcinogen. In so doing the framework promotes a structured approach to the assessment of the overall weight of evidence for a postulated mode of action. By using a defined procedure, which mandates clear and consistent documentation of both the reasoning used and inconsistencies and uncertainties in the available data, the framework brings transparency to the analysis and thereby helps to promote confidence in the conclusions reached. In the IPCS conceptual framework the thought processes involved in making use of mechanistic data in cancer risk assessment are recorded in a structured way. The main components of the framework are as follows:

- postulated mode of action (for induction of a specific animal tumour);
- key events (measurable events critical to tumour induction);
- dose–response relationships;
- temporal association;
- strength, consistency and specificity of association of tumour response with key events (discussion of weight of evidence linking key events, precursor lesions and the tumour response);
- biological plausibility and coherence;
- overall assessment of the postulated mode of action; and,
- consideration of uncertainties, inconsistencies and data gaps.

Essentially these are the elements that are used in assessing the weight of evidence for a postulated mode of action of a chemical carcinogen.

The framework has been widely distributed to regulatory agencies worldwide and is being used nationally (e.g. in the UK (by the Health and Safety Executive, the Advisory Committee on Pesticides etc), Canada, USA, Australia), in the European Union (Existing Substances Regulation) and by international groups such as the Food and Agricultural Organization/World Health Organization Joint Meeting on Pesticide Residues.

3 Risk assessment

3.1 Genotoxic carcinogens

For genotoxic carcinogens, it is theoretically possible that 'one' hit in DNA may induce a mutation leading to clonal transformation of somatic (or germ) cells, eventually resulting in a malignant tumour. In practice this is most unlikely, as numerous protective mechanisms are in place (detoxification of active metabolites, repair of damage before it is fixed by cell replication etc). However, it is not possible, in practice, to identify a threshold level below which no effect would be expected. Thus it is prudent to assume that for genotoxic carcinogens there is not a threshold dose below which no carcinogenic effects occur.

The calculation of cancer risk to humans from animal bioassay data is problematic. There are a number of mathematical models that use dose-response curves to extrapolate from the relatively high dose levels used in animal studies in order to estimate probable responses at lower doses. Such extrapolation is necessary to give an estimate of the likely risk of cancer at low levels of exposure or to predict the level of exposure over a lifetime that would give rise to an increase in incidence of cancer of, for example, one person in 10^6. However, although it is only practical to conduct long-term bioassays in rodents, extrapolation from high dose rodent data to humans is very uncertain. Thus these models may give an impression of precision that cannot be justified in the light of the approximations and assumptions on which they were based. The UK does not therefore support the use of such models for quantitative risk assessment of chemical carcinogens. The reasons given in the COC guidelines in 1991 (DH, 1991) are still valid: the methods are not validated; they are often based on incomplete or inappropriate data, and derived more from mathematical assumptions than from knowledge of biological mechanisms; and they demonstrate a disturbingly wide variation in the risk estimates, depending on the models used.

As both an acceptable daily intake (ADI) and a tolerable daily intake (TDI) are based on the assumption that there is a threshold level below which no effect occurs, and as no threshold level can be determined for a genotoxic carcinogen, no ADIs or TDIs can be established for genotoxic carcinogens or mutagens with *in vivo* activity.

The policy generally adopted in the UK for risk management of such compounds does not rely on quantitative estimates of risk; instead it is based on eliminating exposures or reducing exposures so that they are as low as is reasonably practical.

3.2 Non-genotoxic carcinogens

As non-genotoxic carcinogens are believed to induce tumours as a secondary event following an effect that has a threshold (such as sustained cell proliferation, enzyme induction etc), emphasis is placed on understanding their mode of action, and risk assessment is based on the no-effect level for a key precursor event. Uncertainty (safety) factors are used to determine an ADI or TDI or to identify a reasonable margin of safety.

A separate document 'Uncertainty factors: Principles for their use in Government' is currently being developed by the IGHRC that considers how UK government departments/agencies address uncertainties in human health hazard assessment for chemicals having toxic effects for which a threshold is assumed. This will include the issue of how uncertainty (safety) factors are derived.

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Annex

Glossary

ADI – Acceptable Daily Intake

An estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risks.

Aneugenicity

The ability to induce aneuploidy. This is when the total number of chromosomes within a cell is not an exact multiple of the normal haploid number. Chromosomes may be lost or gained during cell division.

Bias

In the context of epidemiology studies, bias is the operation of factors in the design or execution of the study that leads erroneously to a stronger or weaker association between disease and risk than in fact exists in the underlying population. Examples are selection bias (whereby cases of disease and of the comparison group are chosen differently from the underlying population) and recall bias (where information on exposure is obtained by interview in a non-comparable way from the two groups).

Clastogenicity

The ability to induce chromosome breaks and other structural aberrations such as translocations. Clastogenic events play an important part in the development of some tumours.

Confounding

In the context of epidemiology studies, confounding is the process by which a non-causal association between two factors is produced by a third factor known as a confounder. To be a confounder a factor must be associated both with exposure to the suspect causal agent and also with the disease under investigation; e.g. coffee drinking and bladder cancer, since there is close correlation between coffee drinking and cigarette smoking in many populations.

Chromosome

In prokaryotes the circular DNA molecule containing the entire genetic material of the cell. In eukaryotes one of the threadlike structures in the nucleus carrying the genetic information arranged in a linear sequence.

Genotoxic (or genotoxicity)

Terms that refers to agents that interact with DNA and/or the cellular apparatus that regulates the fidelity of the genome; e.g. the spindle apparatus and enzymes such as the topoisomerases. They are broad terms that include mutation as well as damage to DNA or the production of DNA adducts by the chemical itself or its metabolites. The detection of such effects by themselves does not provide direct evidence of inherited mutations.

Genotoxic carcinogen

A term used to describe those chemicals that are carcinogenic and also give positive results in genotoxicity tests and whose mechanism of carcinogenesis involves mutagenesis as a key initial event.

Mutation

A permanent change in the amount or structure of the genetic material in an organism that can result in a change in the phenotypic characteristics of the

organism. The alteration 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 basis (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.

Neoplasm

Synonym for tumour — see Tumour.

TDI — Tolerable Daily Intake

An estimate of the amount of contaminant, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risks.

Tumour

A mass of abnormal, disorganised cells, arising from pre-existing tissue, which are characterised by excessive and uncoordinated proliferation and by abnormal differentiation. 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. 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 recognisable 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: *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; 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.

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Risk Assessment and Toxicology Steering Committee publications

cr 1 Developing New Approaches to Assessing Risk to Human Health from Chemicals

cr 2 Risk Assessment Approaches used by UK Government for Evaluating Human Health Effects of Chemicals

cr 3 Risk Assessment Strategies in Relation to Population Subgroups

cr 4 Physiologically-Based Pharmacokinetic Modelling: A Potential Tool for Use in Risk Assessment

cr 5 Exposure Assessment in the Evaluation of Risk to Human Health

cr 6 From Risk Assessment to Risk Management: Dealing with Uncertainty

The Interdepartmental Group on Health Risks from Chemicals (IGHRC) publications

cr 7 The Interdepartmental Group on Health Risks from Chemicals: First Report and Forward Plan to 2002

cr 7A The Interdepartmental Group on Health Risks from Chemicals: Annexes to First Report and Forward Plan to 2002

cr 8 Assessment of Chemical Carcinogens: Background to General Principles of a Weight of Evidence Approach

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