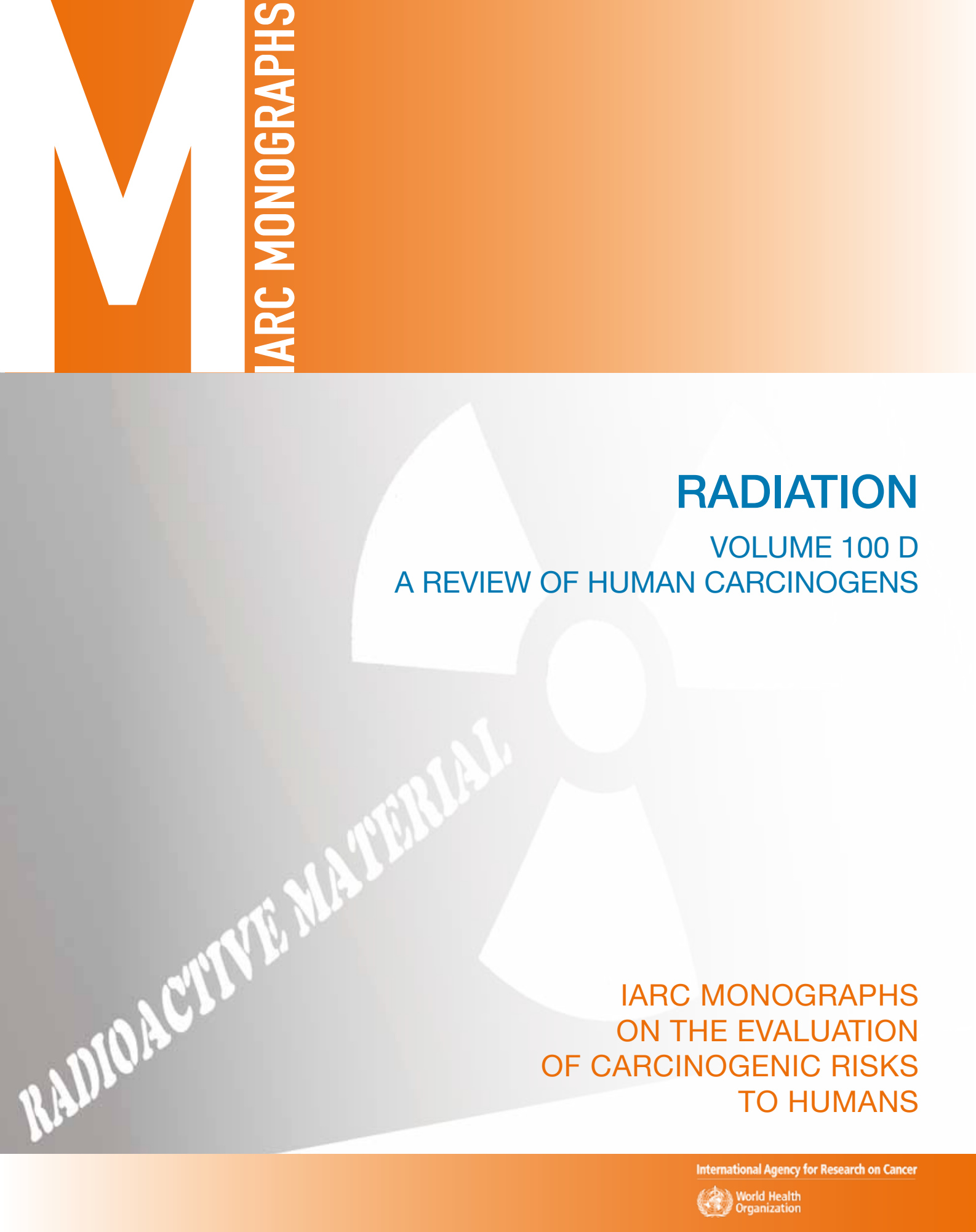
IARC MONOGRAPHS

RADIATION

VOLUME 100 D
A REVIEW OF HUMAN CARCINOGENS



IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

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VOLUME 100 D
A REVIEW OF HUMAN CARCINOGENS

RADIOACTIVE MATERIAL

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 2-9 June 2009

LYON, FRANCE - 2012

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In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the Health, Safety and Hygiene at Work Unit of the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities, and since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the U.S. National Cancer Institute, the U.S. National Institute of Environmental Health Sciences, the U.S. Department of Health and Human Services, or the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities.

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Lorenzo Tomatis (1929-2007)
Founder of the *IARC Monographs* Programme

Lorenzo Tomatis, MD, with other colleagues knowledgeable in primary prevention and environmental carcinogenesis, perceived in the 1960s the growing need to objectively evaluate carcinogenic risks by international groups of experts in chemical carcinogenesis. His vision and determination to provide a reliable source of knowledge and information on environmental and occupational causes of cancer led to his creating the *IARC Monographs* Programme for evaluating cancer risks to humans from exposures to chemicals. The first meeting, held in Geneva in December 1971, resulted in Volume 1 of the IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man [1972], a series known affectionately since as the "orange books". As a champion of chemical carcinogenesis bioassays, Tomatis defined and promoted the applicability and utility of experimental animal findings for identifying carcinogens and for preventing cancers in humans, especially in workers and children, and to eliminate inequalities in judging cancer risks between industrialized and developing countries. Tomatis' foresight, guidance, leadership, and staunch belief in primary prevention continued to influence the *IARC Monographs* as they expanded to encompass personal habits, as well as physical and biological agents. Lorenzo Tomatis had a distinguished career at the Agency, arriving in 1967 and heading the Unit of Chemical Carcinogenesis, before being Director from 1982 to 1993.

Volume 100 of the *IARC Monographs* Series is respectfully dedicated to him.

(photo: Roland Dray)

CONTENTS

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Monographs* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

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[3] Dr Hall's research unit receives funds (not exceeding 5% of total research support) from Electricité de France, an electric power company.
[4] Dr Hoel is providing assistance to Exxon Corp in court cases involving personal injury claimed to be related to radiation. He owns stock in Duke Energy Corp, an electric power company. His university salary is supported in part by grants from the U.S. National Aeronautics and Space Administration (NASA) and the U.S. Department of Energy.
[5] Dr Little wrote software for the British Nuclear Group to calculate risks for workers in the nuclear industry. This represented less than 5% of his annual total professional compensation for 2006 and 2007, when the activity ceased. He also advised the International Epidemiology Institute (USA) and Westlakes Research Institute (UK) on epidemiological matters. This represented less than 5% of total professional income, and work ceased in 2007 for both contracts.
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[7] Dr Mitchel is retired from, and continues to consult for, Atomic Energy of Canada Ltd, a Crown corporation of Canada whose mandate is to sustain and enhance nuclear technology, to manage nuclear wastes, and to maximize return on investment in nuclear technology. The corporation also produces more than half of the world's medical isotopes.
[8] Dr Muirhead manages a section at the Health Protection Agency that receives partial funding from the UK Ministry of Defence to maintain an epidemiological database of nuclear test veterans.
New address: Institute of Health and Society, Newcastle University, UK.
[9] Dr Priest is a manager at Atomic Energy of Canada Ltd, a Crown corporation of Canada whose mandate is to sustain and enhance nuclear technology, to manage nuclear wastes, and to maximize return on investment in nuclear technology. The corporation also produces a significant fraction of the world's medical isotopes.
[10] Dr Richardson provided written testimony on behalf of four persons seeking compensation for diseases claimed to be related to X-rays. He reports receiving no compensation for this case.
[11] Dr Riddell is employed by Westlakes Scientific Consulting Ltd, a consulting firm specializing in the nuclear industry.

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[12] Dr Ullrich provided assistance to Raytheon Co in a court case involving thyroid and kidney cancer claimed to be related to X-rays.

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate

or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme web site (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

For most chemicals and some complex mixtures, the major collection of data and the preparation of working papers for the sections on chemical and physical properties, on analysis, on production and use, and on occurrence are carried out under a separate contract funded by the US National Cancer Institute. Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data
Studies of cancer in humans
Studies of cancer in experimental animals
Mechanistic and other relevant data
Summary
Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production,

which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in

particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — 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 or may not be more appropriate than those with national rates. Internal comparisons of

frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of 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 have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal

relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and

coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo

transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel et al., 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls,

particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of

greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals in vivo indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme web site (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and

the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity*:** A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity*:** The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity*:** There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In

addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:** The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:** Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics,

physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental

animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity*

in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

Part D of Volume 100 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* considers all forms of radiation that were classified as *carcinogenic to humans (Group 1)* in Volumes 1–99.

Volume 100 – General Information

About half of the agents classified in Group 1 were last reviewed more than 20 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent epidemiological studies and animal cancer bioassays have demonstrated that many cancer hazards reported in earlier studies were later observed in other organs or through different exposure scenarios. Much can be learned by updating the assessments of agents that are known to cause cancer in humans. Accordingly, IARC has selected *A Review of Human Carcinogens* to be the topic for Volume 100. It is hoped that this volume, by compiling the knowledge accumulated through several decades of cancer research, will stimulate cancer prevention activities worldwide, and will be a valued resource for future research to identify other agents suspected of causing cancer in humans.

Volume 100 was developed by six separate Working Groups:

Pharmaceuticals
Biological agents
Arsenic, metals, fibres, and dusts
Radiation
Personal habits and indoor combustions
Chemical agents and related occupations

Because the scope of Volume 100 is so broad, its *Monographs* are focused on key information. Each *Monograph* presents a description of a carcinogenic agent and how people are exposed, critical overviews of the epidemiological studies and animal cancer bioassays, and a concise review of the toxicokinetic properties of the agent, plausible mechanisms of carcinogenesis, and potentially susceptible populations, and life-stages. Details of the design and results of individual epidemiological studies and animal cancer bioassays are summarized in tables. Short tables that highlight key results appear in the printed version of Volume 100, and more extensive tables that include all studies appear on the website of the *IARC Monographs* programme (http://monographs.iarc.fr). For a few well-established associations (for example, tobacco smoke and human lung cancer), it was impractical to

include all studies, even in the website tables. In those instances, the rationale for inclusion or exclusion of sets of studies is given.

Each section of Volume 100 was reviewed by a subgroup of the Working Group with appropriate subject expertise; then all sections of each *Monograph* were discussed together in a plenary session of the full Working Group. As a result, the evaluation statements and other conclusions reflect the views of the Working Group as a whole.

Volume 100 compiles information on tumour sites and mechanisms of carcinogenesis. This information will be used in two scientific publications that may be considered as annexes to this volume. One publication, *Tumour Site Concordance between Humans and Experimental Animals*, will analyse the correspondence of tumour sites among humans and different animal species. It will discuss the predictive value of different animal tumours for cancer in humans, and perhaps identify human tumour sites for which there are no good animal models. Another publication, *Mechanisms Involved in Human Carcinogenesis*, will describe mechanisms known to or likely to cause cancer in humans. Joint consideration of multiple agents that act through similar mechanisms should facilitate the development of a more comprehensive discussion of these mechanisms. Because susceptibility often has its basis in a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents acting through each mechanism. This publication will also suggest biomarkers that could render future research more informative. In this way, IARC hopes that Volume 100 will serve to improve the design of future cancer studies.

Specific remarks about the review of radiation in this volume

Solar radiation was classified as Group 1 in Volume 55 (IARC, 1992). At that time, some individual components of solar radiation, ultraviolet radiation A, B, and C, were classified as *probably carcinogenic to humans (Group 2A)*, along with sunlamps and sunbeds, which act as artificial sources of ultraviolet radiation. These agents are also reviewed in this volume to evaluate whether the epidemiological and mechanistic studies available today provide sufficient evidence to identify specific components of solar radiation as carcinogenic to humans. In Volume 75 (IARC, 2000), X-radiation and γ-radiation were classified as Group 1, along with neutrons. Internalized radionuclides that emit α particles or β particles were classified as Group 1 in Volume 78 (IARC, 2001). That volume also listed individually in Group 1 specific radionuclides for which there was sufficient evidence in humans. Of these, radon-222 and its decay products had been classified earlier as Group 1 in Volume 43 (IARC, 1988). One occupation involving radiation exposure, underground haematite mining with exposure to radon, was reviewed in Volume 1 (IARC, 1972) and classified as Group 1 in Supplement 7 (IARC, 1987).

In conducting this combined review of different types of ionizing radiation from various sources – resulting in a separate Group-1 classification for each of these types – the Working Group discussed the suggestion to arrive at a generic evaluation of the cancer hazards from exposure to radiation in the high-energy region of the electromagnetic spectrum (wavelength, <10 nm).

The Working Group considered that all types of ionising radiation, including the neutron particle, transfer their energy to biological material as either separate or clustered ionization and excitation events, primarily through a free–electron-mediated mechanism. Furthermore, the deposition

of energy from all types of ionizing radiation results in a wide variety of molecular damage in the cell, including base damage and single- and double-strand breaks in DNA, some of which may be clustered and form complex lesions. Subsequent processing of these lesions may lead to chromosomal aberrations and mutations. And finally, there is ample evidence that damage to DNA is indeed of primary importance in the biological outcome of exposure to ionising radiation. On the basis of these considerations, the Working Group reached the final evaluation that "All types of ionizing radiation are *carcinogenic to humans (Group 1)*"

In reviewing studies on occupational exposures to ultraviolet radiation, the Working Group found strong evidence of ocular melanoma in welders. After a literature search for other studies of welders and a review of this information, the Working Group concluded that these studies provide sufficient evidence of carcinogenicity. Welding fumes had been classified as *possibly carcinogenic to humans (Group 2B)* in Volume 49 (IARC, 1990) and this was not scheduled for update in this volume. A full review of welding was considered to be outside the scope of this meeting, as concern about welding has generally focused on exposures to mixtures of metal and chemical fumes (IARC, 1990). Welders and people who work with them may also be exposed to fumes of thorium-232, which is used in tungsten welding rods (NCRP, 1988; Nuclear Regulatory Commission, 2001). Although it is not possible without a full review to attribute the occurrence of ocular melanoma to ultraviolet radiation specifically, the review of ocular melanoma in this volume was thorough and the findings are expected to remain after a full review of welding in a subsequent *Monograph*. Accordingly, the Working Group made an evaluation that there is *sufficient evidence* in humans for the carcinogenicity of welding.

A summary of the findings of this volume appears in The Lancet Oncology (El Ghissassi *et al.*, 2009).

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SOLAR AND ULTRAVIOLET RADIATION

Solar and ultraviolet radiation were considered by a previous IARC Working Group in 1992 (IARC, 1992). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Terrestrial life is dependent on radiant energy from the sun. Solar radiation is largely optical radiation [radiant energy within a broad region of the electromagnetic spectrum that includes ultraviolet (UV), visible (light) and infrared radiation], although both shorter wavelength (ionizing) and longer wavelength (microwaves and radiofrequency) radiation is present. The wavelength of UV radiation (UVR) lies in the range of 100–400 nm, and is further subdivided into UVA (315–400 nm), UVB (280–315 nm), and UVC (100–280 nm). The UV component of terrestrial radiation from the midday sun comprises about 95% UVA and 5% UVB; UVC and most of UVB are removed from extraterrestrial radiation by stratospheric ozone.

Approximately 5% of solar terrestrial radiation is UVR, and solar radiation is the major source of human exposure to UVR. Before the beginning of last century, the sun was essentially the only source of UVR, but with the advent of artificial sources the opportunity for additional exposure has increased.

1.1 Nomenclature and units

For the purpose of this *Monograph*, the photobiological designations of the Commission Internationale de l'Eclairage (CIE, International Commission on Illumination) are the most relevant, and are used throughout to define the approximate spectral regions in which certain biological absorption properties and biological interaction mechanisms may dominate (Commission Internationale de l'Eclairage, 1987).

Sources of UVR are characterized in radiometric units. The terms dose (J/m^2) and dose rate (W/m^2) pertain to the energy and power, respectively, striking a unit surface area of an irradiated object (Jagger, 1985). The radiant energy delivered to a given area in a given time is also referred to as 'fluence', 'exposure dose' and 'dose' (see IARC, 1992 for further details).

A unit of effective dose [dose weighted in accordance with its capacity to bring about a particular biological effect] commonly used in cutaneous photobiology is the 'minimal erythemal dose' (MED). One MED has been defined as the lowest radiant exposure to UVR that is sufficient to produce erythema with sharp margins 24 hours after exposure (Morison, 1983). Another end-point often used in cutaneous

photobiology is a just-perceptible reddening of exposed skin; the dose of UVR necessary to produce this 'minimal perceptible erythema' is sometimes also referred to as a MED. In unacclimatized, white-skinned populations, there is an approximately 4-fold range in the MED of exposure to UVB radiation (Diffey & Farr, 1989). When the term MED is used as a unit of 'exposure dose', a representative value for sun-sensitive individuals of 200 J/m^2 is usually chosen. Since 1997, the reference action spectrum for erythema on human skin (McKinlay & Diffey, 1987) has become an International Standards Organization (ISO)/CIE norm, which, by convolution with the emission spectrum of any UVR source, enables the calculation of the erythemal yield of the source. A Standard Erythema Dose (SED) has been proposed as a unit of erythemally effective UVR dose equivalent to 100 J/m^2 (Commission Internationale de l'Eclairage, 1998).

Notwithstanding the difficulties of interpreting accurately the magnitude of such imprecise units as the MED and the SED, they have the advantage over radiometric units of being related to the biological consequences of the exposure.

The UV index is a tool intended for the communication of the UVR intensity to the general public. It has been developed jointly by the World Health Organization, the United Nations Environment Program, the International Commission on Non-Ionizing Radiation Protection and was standardized by ISO/CIE. It expresses the erythemal power of the sun as follows:

UV Index = 40 times the erythemally effective power of the sun in W/m^2

The clear sky UV Index at solar noon is generally in the range of 0–12 at the Earth's surface, with values over 11 being considered extreme.

1.2 Methods for measuring UVR

UVR can be measured by chemical or physical detectors, often in conjunction with a monochromator or band-pass filter for wavelength selection. Physical detectors include radiometric devices, which respond to the heating effect of the radiation, and photoelectric devices, in which incident photons are detected by a quantum effect such as the production of electrons. Chemical detectors include photographic emulsions, actinometric solutions and UV-sensitive plastic films.

The solar UV irradiation of large portions of the Earth is currently measured using multifrequency imaging detectors on meteorological satellites.

1.3 Sources and exposure

1.3.1 Solar UVR

Optical radiation from the sun is modified substantially as it passes through the Earth's atmosphere, although about two-thirds of the energy from the sun that enters the atmosphere penetrates to ground level. The annual variation in extraterrestrial radiation is less than 10%; the variation in the modifying effect of the atmosphere is far greater (Moseley, 1988).

On its path through the atmosphere, solar UVR is absorbed and scattered by various constituents of the atmosphere. It is scattered by air molecules, particularly oxygen and nitrogen, by aerosol and dust particles, and is scattered and absorbed by atmospheric pollution. Total solar irradiance and the relative contributions of different wavelengths vary with altitude. Clouds attenuate solar radiation, although their effect on infrared radiation is greater than on UVR. Reflection of sunlight from certain ground surfaces may contribute significantly to the total amount of scattered UVR (Moseley, 1988).

The levels of solar UVB radiation reaching the surface of the Earth are largely controlled

by the stratospheric ozone layer, which has been progressively depleted as a result of accumulation of ozone-destroying chemicals in the Earth's atmosphere – mostly chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs), whose main use has been in refrigeration and air-conditioning. The accumulation of ozone-depleting chemicals in the atmosphere ceased largely as a result of the Montreal Protocol on "Substances that deplete the ozone layer," which was opened for signature in 1987, and has been ratified by 196 states.

Global climate change due to the accumulation of carbon dioxide (CO_2) in the atmosphere can also adversely affect stratospheric ozone. This will influence whether, when, and to what extent ozone levels will return to pre-1980 values. The current best estimate is that global (60°S–60°N) ozone levels will return to pre-1980 levels around the middle of the 21st century, at or before the time when stratospheric concentrations of ozone-depleting gases return to pre-1980 levels. Climate change will also influence surface UV radiation through changes induced mainly to clouds and the ability of the Earth's surface to reflect light. Aerosols and air pollutants are also expected to change in the future. These factors may result in either increases or decreases of surface UV irradiance, through absorption or scattering. As ozone depletion becomes smaller, these factors are likely to dominate future UV radiation levels (World Meteorological Organization, 2007).

The amount of solar UVR measured at the Earth's surface depends upon several factors as follows:

- *Time of day*: In summer, about 20–30% of the total daily amount of UVR is received between 11:00 and 13:00, and 75% between 9:00 and 15:00 (sun time not local time; Diffey, 1991).
- *Season*: Seasonal variation in terrestrial UV irradiance, especially UVB, at the Earth's surface is significant in temperate regions but much less nearer the equator (Diffey, 1991).
- *Geographic latitude:* Annual UVR exposure dose decreases with increasing distance from the equator (Diffey, 1991).
- *Altitude:* In general, each 300 metre increase in altitude increases the sunburning effectiveness of sunlight by about 4% (Diffey, 1990).
- *Clouds:* Clouds influence UV ground irradiance, through reflection, refraction, absorption and scattering, and may increase or, more usually, decrease UV ground irradiance. Complete light cloud cover prevents about 50% of UVR energy from reaching the surface of the Earth (Diffey, 1991). Very heavy cloud cover absorbs and can virtually eliminate UVR even in summer. Even with heavy cloud cover, however, the scattered UVR component of sunlight (as opposed to that coming directly from the sun) is seldom less than 10% of that under clear sky. While most clouds block some UV radiation, the degree of protection depends on the type and amount of clouds; some clouds can actually increase the UV intensity on the ground by reflecting, refracting and scattering the sun's rays. For example, under some circumstances (haze, cirrus skies, solar zenith angles ranging from 40–63°), the solar irradiance at Toowoomba, Australia (27.6°S, 151.9°E), was found to be 8% greater than that of an equivalent clear sky (Sabburg & Wong, 2000; Sabburg *et al.*, 2001).
- *Surface reflection:* The contribution of reflected UVR to a person's total UVR exposure varies in importance with several factors. A grass lawn scatters 2–5% of incident UVB radiation. Sand reflects about 10–15%, so that sitting under an umbrella on the beach can lead to sunburn both from scattered UVB from the

sky and reflected UVB from the sand. Fresh snow may reflect up to 85–90% of incident UVB radiation while water, in particular white foam in the sea, may reflect up to 30%. Ground reflectance is important, because parts of the body that are normally shaded are exposed to reflected radiation (Diffey, 1990).

- *Air pollution:* Tropospheric ozone and other pollutants can decrease UVR.

(a) Measurements of terrestrial solar radiation

Because UVR wavelengths between about 295–320 nm (UVB radiation) in the terrestrial solar spectrum are thought to be those mainly responsible for adverse health effects, several studies have focused on this spectral region. Accurate measurements of UVR in this spectral band are difficult to obtain, however, because the spectral curve of terrestrial solar irradiance increases by a factor of more than five between 290–320 nm. Nevertheless, extensive measurements of ambient UVR in this spectral band have been made worldwide. Measurements of terrestrial solar UVA are less subject to error than measurements of UVB, because the spectrum does not vary widely with zenith angle and the spectral irradiance curve is relatively flat (IARC, 1992).

The total solar radiation that arrives at the Earth's surface is termed 'global radiation'. Global radiation is made up of two components, referred to as 'direct' and 'diffuse'. Approximately 70% of the UVR at 300 nm is in the diffuse component rather than in the direct rays of the sun. The ratio of diffuse to direct radiation increases steadily from less than 1.0 at 340 nm to at least 2.0 at 300 nm. UVR reflected from the ground (the albedo) may also be important (IARC, 1992).

Solar UV levels reaching the Earth's surface can now be measured by satellites using hyperspectral imaging to observe solar backscatter radiation in the visible and ultraviolet ranges. NASA's Total Ozone Mapping Spectrometer (TOMS) device was installed on several spacecraft, including the Earth Probe spacecraft for collecting data during 1996–2005. TOMS is no longer available but the continuity of satellite-derived global UV data is maintained via the new Ozone Monitoring Instrument (OMI), on board the Aura satellite (http://aura.gsfc.nasa.gov/index.html). The presence of aerosols, clouds and snow or ice cover can lead to significant biases, and new algorithms have been developed to improve the satellite-derived measurement of surface UV irradiance using Advanced Very High Resolution Radiometer (AVHRR) and Meteosat images. Currently the European Solar Data Base (SoDa) is capable to perform on-the-fly fast interpolation with a non-regular grid and to provide data for any geographic site with a limitation to a 5-km grid cell. The SoDa contains information going back to the year 1985, available at http://www.soda-is.com/eng/services/services_radiation_free_eng.php.

Satellite data have been used to draw maps of UV exposure, and are available for use for epidemiological and other purposes. For example, data sets of UV irradiance derived from TOMS data for the period 1979 to 2000 are available by date, latitude and longitude for UVB and UVA. Data from satellites and ground-level measurements show that UV irradiation does not vary steadily with latitude but that local conditions may greatly influence actual UV irradiation levels (a good example of this situation may be found in the extremely elevated UV levels recorded in the summer 2003 during the heat wave that killed thousands of people in France and Northern Italy).

(b) Personal exposures

Individual sun exposure can be estimated through questionnaires, which are at best semi-quantitative, and do not give any detailed

information on the wavelength of UV exposure. Individual UV dosimeters have been used in epidemiological studies, but cannot be used for the large-scale monitoring of UV exposure of populations.

Exposure data for different anatomical sites is of value in developing biological dose–response relationships. The exposure of different anatomical sites to solar UVR depends not only on ambient UVR and the orientation of sites with respect to the sun, but also on cultural and social behaviour, type of clothing, and use of sunscreen. The most exposed skin surfaces, such as the nose, tops of the ears and forehead, have levels of UVB exposure that range up to one order of magnitude relative to that of the lesser exposed areas, such as underneath the chin. Ground reflectance plays a major role in exposure to UVB of all exposed body parts, including the eye and shaded skin surfaces, particularly with highly reflective surfaces such as snow. The solar exposure of the different anatomical sites of outdoor workers has recently been calculated (Milon *et al.*, 2007) [Computerised models that integrate direct, diffuse and reflected radiation are currently being developed].

Sunscreens can be applied to control the dose of UVR to exposed skin. While undoubtedly useful when sun exposure is unavoidable (IARC, 2001), their use may lead to a longer duration of sun exposure when sun exposure is intentional (Autier *et al.*, 2007).

The cumulative annual exposure dose of solar UVR varies widely among individuals in a given population, depending to a large extent on the occupation and extent of outdoor activities. For example, it has been estimated that indoor workers in mid-latitudes (40–60°N) receive an annual exposure dose of solar UVR to the face of about 40–160 times the MED, depending on their level of outdoor activities, whereas the annual solar exposure dose for outdoor workers is typically around 250 times the MED. Because few actual measurements of personal exposures have been reported, these estimates should be considered to be very approximate. They are also subject to differences in cultural and social behaviour, clothing, occupation, and outdoor activities.

1.3.2 Artificial sources of UVR

Cumulative annual outdoor exposure may be increased by exposure to artificial sources of UVR. Indoor tanning is a widespread practice in most developed countries, particularly in northern Europe and the United States of America, and is gaining popularity even in sunny countries like Australia. The prevalence of indoor tanning varies greatly among different countries, and has increased during the last decades (IARC, 2006a). The majority of users are young women, and a recent survey indicated that in the USA, up to 11% of adolescents aged 11–years had ever used an indoor tanning device (Cokkinides *et al.*, 2009). The median annual exposure dose from artificial tanning is probably 20–30 times the MED. Prior to the 1980s, tanning lamps emitted high proportions of UVB and even UVC. Currently used appliances emit primarily UVA; and in countries where tanning appliances are regulated (e.g. Sweden and France), there is a 1.5% upper limit UVB. However, commercially available "natural" UV-tanning lamps may emit up to 4% UVB. UV emission of a modern tanning appliance corresponds to an UV index of 12, i.e. equivalent to midday tropical sun (IARC, 2006a).

Other sources of exposures to UVR include medical and dental applications. UVR has been used for several decades to treat skin diseases, notably psoriasis. A variety of sources of UVR are used, emitting either broad-band UVA or narrow-band UVB. A typical dose in a single course of UVB phototherapy can be in the range of 200–300 times the MED (IARC, 2006a).

UVR is also used in many different industries, yet there is a paucity of data concerning human exposure from these applications,

probably because in normal practice, sources are well contained and exposure doses are expected to be low. In some settings, workers may be exposed to radiation by reflection or scattering from adjacent surfaces. Staff in hospitals who work with unenclosed phototherapy equipment are at potential risk of overexposure unless protective measures are taken. Indoor tanning facilities may comprise 20 or more UVA tanning appliances, thus potentially exposing operators to high levels (> 20W/m^2) of UVA (IARC, 2006a).

Acute overexposures to the eyes are common among electric arc welders. Individuals exposed to lighting from fluorescent lamps may typically receive annual exposure doses of UVR in the range of 0–30 times the MED, depending on illuminance levels and whether or not the lamps are housed behind plastic diffusers. It is also worth noting that tungsten–halogen lamps used for general lighting may emit broad-band UVR (including UVC) when not housed behind a glass filter.

2. Cancer in Humans

2.1 Natural sunlight

2.1.1 Basal cell carcinoma and cutaneous squamous cell carcinoma

In the previous *IARC Monograph* (IARC, 1992), the evaluation of the causal association of basal cell carcinoma and squamous cell carcinoma with solar radiation was based on descriptive data in Caucasian populations, which showed positive associations with birth and/or residence at low latitudes and rare occurrence at non-sun-exposed anatomical sites. The evaluation was also based on case–control and cohort studies whose main measures were participants' retrospectively recalled sun exposure. The majority of analyticalal studies published since have also used recalled amount of sun exposure, though some more recent studies have made objective measures of ambient UV and used clinical signs of cumulative UV damage to the skin such as solar lentigines and actinic keratoses (Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.1.pdf, Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.2.pdf, and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.3.pdf).

With regard to basal cell carcinoma, all studies except one (Corona *et al.*, 2001) showed significant positive associations with sunburns at some stage of life or overall. Of the studies that collected information on the presence of actinic keratoses (Green *et al.*, 1996; Corona *et al.*, 2001; Walther *et al.*, 2004; Pelucchi *et al.*, 2007), all showed this also to be a strong risk factor (Tables 2.1 and 2.3 on-line). It was proposed that the association of basal cell carcinoma with sun exposure may vary by histological subtype and anatomical site (Bastiaens *et al.*, 1998). Although a case–control study showed this variation for recalled sun exposure (Pelucchi *et al.*, 2007), a cohort study did not (Neale *et al.*, 2007).

For squamous cell carcinoma, while case–control studies tended to demonstrate little association with sunburns (Table 2.2 on-line), cohort studies uniformly showed significant positive associations (Table 2.3 on-line). The presence of actinic keratoses, a proportion of which are squamous cell carcinoma precursors, was the strongest risk factor identified (Table 2.3 on-line; Green *et al.*, 1996).

2.1.2 Cutaneous malignant melanoma

Cutaneous malignant melanoma occurs in the pigment cells of the skin. Until 10–15 years ago, with the exception of two histological subgroups, melanoma was usually regarded as a single entity in analytical studies assessing the association with sunlight. The two subgroups,

lentigo maligna melanoma and acral lentiginous melanoma, were usually excluded from studies, the former paradoxically because of its known causal link with cumulative sun exposure, the latter for the opposite reason because it typically occurs on the soles of the feet.

In the previous *IARC Monograph* (IARC, 1992), the evaluation of the causal association between solar radiation and melanoma was based on descriptive data and on data from case–control studies. The main measures of exposure were participants' recalled sun exposure. 'Intermittent' sun exposure, which loosely equated with certain sun-intensive activities, such as sunbathing, outdoor recreations, and holidays in sunny climates, generally showed moderate-to-strong positive associations with melanoma. However, 'chronic' or 'more continuous' exposure, which generally equated with 'occupational' exposure, and total sun exposure (sum of 'intermittent'+'chronic'), generally showed weak, null or negative associations.

These results were collectively interpreted under the 'intermittent sun exposure' hypothesis (Fears *et al.*, 1977) as showing that melanoma occurs as a result of a pattern of intermittent intense sun exposure rather than of more continuous sun exposure. Studies that had also assessed objective cutaneous signs of skin damage that were generally assumed to be due to accumulated sun exposure, e.g. presence or history of actinic keratoses, or signs of other sun-related skin damage, showed, almost uniformly, strong positive associations with melanoma. This inconsistency of evidence with the apparently negative associations of reported 'chronic' sun exposure with melanoma was noted but not satisfactorily explained.

Several systematic reviews and meta-analyses of analytical studies of the association of melanoma with sun exposure have been published since (Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.4.pdf). The summary melanoma relative risk (RR) estimates of one of the largest meta-analyses, based on 57 studies published up to September 2002 (Gandini *et al.*,, 2005a, b) were: sunburn (ever/never), 2.0 (95%CI: 1.7–2.4); intermittent sun exposure (high/low), 1.6 (95%CI: 1.3–2.0); chronic sun exposure (high/low), 1.0 (95%CI: 0.9–1.0); total sun exposure (high/low), 1.3 (95%CI: 1.0–1.8); actinic tumours (present, past/none), 4.3 (95%CI: 2.8–6.6).

Case–control studies and the cohort study (Veierød *et al.*, 2003) that have been published since September 2002 have shown results that are generally consistent with the meta-analysis, and have not been included in this review (Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.5.pdf and Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.6.pdf).

(a) Anatomical site of melanoma

Melanoma–sun-exposure associations according to the anatomical site of the melanoma have recently gained greater consideration. Several studies reported differences in age-specific incidence rates by site of melanoma (Holman *et al.*, 1980; Houghton *et al.*, 1980; Elwood & Gallagher, 1998; Bulliard & Cox, 2000). The numerous analytical studies of risk factors by site of melanoma (Weinstock *et al.*, 1989; Urso *et al.*, 1991; Green, 1992; Krüger *et al.*, 1992; Rieger *et al.*, 1995; Whiteman *et al.*, 1998; Carli *et al.*, 1999; Håkansson *et al.*, 2001; Winnepenninckx & van den Oord, 2004; Cho *et al.*, 2005; Purdue *et al.*, 2005; Nikolaou *et al.*, 2008) collectively show that melanomas of the head and neck are strongly associated with actinic keratoses, and melanomas on the trunk are strongly associated with naevi. Similar findings have been reported from recent detailed case–case studies (Whiteman *et al.*, 2003, 2006; Siskind *et al.*, 2005; Lee *et al.*, 2006).

(b) Skin pigmentation

Two observations from epidemiological studies may help explain the paradox of the lack of association of melanoma with chronic sun exposure. First, outdoor workers are not at a substantially increased risk of melanoma (IARC, 1992; Armstrong & Kricker, 2001); second, outdoor workers tend to have a higher-than-average ability to develop a tan (Green *et al.*, 1996; Chang *et al.*, 2009). Outdoor workers tend to be constitutionally protected from solar skin damage and at a lower risk of skin cancer than workers in other occupations because of self-selection based on skin pigmentation. Indeed, such self-selection has been observed in a non-Hispanic white study population from Philadelphia and San Francisco, USA, whereby the average number of hours outdoors in general increases with an increasing ability to tan (Fears *et al.*, 2002). The role of baseline sun sensitivity in influencing sun exposure in the etiology of melanoma has long been recognized (Holman *et al.*, 1986; Nelemans *et al.*, 1995).

(c) Latitude

The assessment and reporting of sun exposure may vary among studies at different latitudes, due to latitude differences in sun exposure opportunity and behaviour (Elwood & Diffey, 1993; Gandini *et al.*, 2005a, b). One approach to avoid the problems of quantifying individual sun exposure at different latitudes has been to use ambient UV flux (Fears *et al.*, 2002; Kricker *et al.*, 2007) for individuals through life, calculated from their residential histories, to accurately quantify at least potential solar UV exposure.

Two case–control studies, both done at comparatively high latitudes (Connecticut, USA; Chen *et al.*, 1996) and (Italy; Naldi *et al.*, 2005), and one pooled analysis stratified by latitude (Chang *et al.*, 2009), have presented site-specific melanoma risk estimates in relation to latitude (see Table 2.5 on-line). Recalls of sunburns throughout life were generally predictive of melanomas at all sites in both case–control studies and in the pooled analysis (RR, 1.0–2.0). Those who had objective signs of cumulative sun damage were at increased risk of melanoma at specific sites: the presence of solar lentigines increased the risk of melanoma on the lower limbs (Naldi *et al.*, 2005; RR, 1.5; 95%CI: 1.0–2.1, with reference to absence of solar lentigines), while actinic keratoses increased the risk of melanoma on the head and neck (Chang *et al.*, 2009; RR, 3.1; 95%CI: 1.4–6.7; based on three studies from high to low latitudes in which solar keratoses were measured). [The Working Group noted that the omission from many studies of the lentigo maligna melanoma subgroup, which is known to be associated with cumulative sun exposure, potentially results in an underestimation of the association with melanomas on the head and limbs.]

2.1.3 Cancer of the lip

Cancer of the lip has been associated with outdoor occupations in several descriptive studies (IARC, 1992). Three early case–control studies reported increases in risk for cancer of the lip with outdoor work, but use of tobacco could not be ruled out as an explanation for this association in any study (Keller, 1970; Spitzer *et al.*, 1975; Dardanoni *et al.*, 1984).

Two case–control studies have been published since that include information on tobacco smoking. The first (Pogoda & Preston-Martin, 1996), which included women only, found increased risks of cancer of the lip with average annual residential UV flux, recalled average annual hours spent in outdoor activities, and having played high-school or college sports; risk estimates were adjusted for complexion, history of skin cancer and average number of cigarettes smoked per day. Risk was not increased in women whose last occupation was outdoors (odds ratio (OR)), 1.2; 95%CI: 0.5–2.8). The dose–response

relationship with recalled average annual hours spent in outdoor activities was inconsistent: with < 30 hours as the reference category, the odds ratios were 2.6 (95%CI: 1.0–6.5) for 30–99 hours; 1.8 (95%CI: 0.7–4.6) for 100–299 hours; and, 4.7 (95%CI: 1.9–12.1) for > 300 hours. The second, which included men only (Perea-Milla López *et al.*, 2003), found no evidence of an increased risk for cancer of the lip with estimates of cumulative sun exposure during leisure time or holiday. Risk was increased with cumulative sun exposure in outdoor work during the summer months, but without any dose–response (OR, 11.7–12.7; with wide confidence intervals). The odds ratios were adjusted for cumulative alcohol and tobacco intake and "leaving the cigarette on the lip," among other things. In a meta-analysis of cancer in farmers (Acquavella *et al.*, 1998), the pooled relative risk for cancer of the lip from 14 studies was 1.95 (95%CI: 1.82–2.09) (*P* for heterogeneity among studies, 0.22). [The Working Group noted that given the relative risks for oesophageal cancer and lung cancer were 0.77 and 0.65, respectively, confounding by smoking was unlikely, but confounding with other farm-related exposures could not be excluded.]

See Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.7.pdf and Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.8.pdf.

2.1.4 Cancer of the eye

(a) Squamous cell carcinoma of the conjunctiva

(i) Descriptive studies

Incidence of squamous cell carcinoma of the eye was inversely correlated with latitude across a wide range of countries (Newton *et al.*, 1996), and directly associated with measured ambient UVB irradiance across the original nine Surveillance Epidemiology and End Results (SEER) cancer registry areas of the USA (Sun *et al.*, 1997).

(ii) Case–control studies

Three small case–control studies included only or mainly cases with conjunctival intraepithelial neoplasia (Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.9.pdf). Napora *et al.* (1990) compared 19 patients with biopsy-proven conjunctival intraepithelial neoplasia (including one with invasive squamous cell carcinoma) with 19 age- and sex-matched controls. The odds ratio for "office work" was 0.21 [95%CI: 0.04–0.99; Fisher Exact 95%CIs calculated from numbers in authors' table]. Lee *et al.* (1994) included 60 [probably prevalent] cases of ocular surface epithelial dysplasia (13 were conjunctival squamous cell carcinoma) diagnosed over 19 years (40% participation), and 60 age- and sex-matched hospital-based controls. Among others, positive associations were observed between ocular surface epithelial dysplasia and history of solar keratoses [OR, for history at < 50 and ≥ 50 years of age combined, 9.4 (95%CI: 2.8–31)] and duration of residence at ≤ 30° south latitude for 31–49 years (OR, 2.2; 95%CI: 0.6–8.3), and for 50 years or more (OR, 3.9; 95%CI: 1.0–14.8) relative to ≤ 30 years. Cumulative years of life in which > 50% of daytime was spent outdoors were similarly but more weakly associated with ocular surface epithelial dysplasia. Tulvatana *et al.* (2003) studied 30 cases of conjunctival squamous cell neoplasia (intraepithelial or invasive) and 30 age- and sex-matched control patients having extracapsular cataract extraction from whom diseased conjunctiva was taken [site of biopsy not specified]. Solar elastosis [representing pathologically proven solar damage] was observed in the conjunctiva of 53% of cases and 3% of controls, resulting in an odds ratio of 16.0 (95%CI: 2.49–671). [The Working Group noted that while pathologists were said to be "masked," it was not stated that tissue sections from cases were free of neoplastic tissue.]

In the only case–control study of exclusively conjunctival squamous cell carcinoma, Newton *et al.* (2002) studied 60 Ugandan patients with a clinical diagnosis of conjunctival squamous cell carcinoma and 1214 controls diagnosed with other cancers not known to be associated with solar UV exposure or infection with HIV, HPV or Kaposi Sarcoma herpesvirus. The risk for conjunctival squamous cell carcinoma increased with "time spent cultivating": with reference to 0–9 hours a week, the odds ratios were 1.9 for 10–19 hours and 2.4 for ≥ 20 hours (P = 0.05), adjusted for age, sex, region of residence, HIV-1 status, and low personal income. Both HIV-1 status and personal income were strong predictors of risk.

(b) Ocular melanoma

(i) Descriptive studies

No increase in the incidence of ocular melanoma was recorded by the US SEER programme during 1974–98, which is in contrast with the increasing incidence of cutaneous melanoma over the same period (Inskip *et al.*, 2003).

Three studies have reported on the distribution of choroidal melanomas within the eye in relation to the presumed distribution of choroidal sun exposures across the choroid. The first of these (Horn *et al.*, 1994), which analysed 414 choroidal, 20 ciliary body and 18 iris melanomas, concluded that choroidal and iris melanomas were located most frequently in "the areas that are presumably exposed to the most sunlight." Specifically, melanomas in the posterior choroid were observed to preferentially involve the central area. The second (Schwartz *et al.*, 1997), which analysed 92 choroidal melanomas, concluded that there was no preferential location for tumours on the choroid, having rigorously estimated "the average dose distribution on the retina received in outdoor daylight." A third study (Li *et al.*, 2000), which analysed 420 choroidal and ciliary body melanomas, mapped incident melanomas on the retina and observed that rates of occurrence were concentrated in the macula area, and decreased progressively with increasing distance from the macula to the ciliary body. It was concluded that this pattern was consistent with the dose distribution of light on the retinal sphere as estimated by Schwartz *et al.* (1997).

(ii) Case–control and cohort studies

Nine case–control studies and one cohort study reported on associations of sun exposure with ocular melanoma (Gallagher *et al.*, 1985; Tucker *et al.*, 1985; Holly *et al.*, 1990; Seddon *et al.*, 1990; van Hees *et al.*, 1994; Pane & Hirst, 2000; Håkansson *et al.*, 2001; Vajdic *et al.*, 2002; Lutz *et al.*, 2005 (incorporating also data from Guénel *et al.*, 2001); and Schmidt-Pokrzywniak *et al.*, 2009). In addition, one previously reported case–control study reported new analyses of occupation and ocular melanoma (Holly *et al.*, 1996; Tables 2.8 and 2.9 on-line).

Four studies (Gallagher *et al.*, 1985; Holly *et al.*, 1990; Seddon *et al.*, 1990; Tucker *et al.*, 1985) found an increased risk for ocular melanoma in people with light skin, light eye colour or light hair colour. Outdoor activities were associated with ocular melanoma in one study (Tucker *et al.*, 1985).

Four studies (Tucker *et al.*, 1985; Seddon *et al.*, 1990; Håkansson *et al.*, 2001; Vajdic *et al.*, 2001, 2002) reported statistically significant associations between a measure of sun exposure and ocular melanoma. Tucker *et al.* (1985) observed an increased risk of ocular melanoma in people born in the south of the USA (south of 40°N) relative to those born in the north (OR, 2.7; 95%CI: 1.3–5.9), which appeared to be independent of duration of residence in the south. Seddon *et al.* (1990) reported on two separate series of cases and controls. In the first series, increased risks of uveal melanoma with residence in the south of the USA were observed (OR, 2.4; 95%CI: 1.4–4.3

for up to 5 years; and OR, 2.8; 95%CI: 1.1–6.9 for more than 5 years). In the second series, the risk increased with increasing years of "intense sun exposure" (OR, 1.5; 95%CI: 1.0–2.2 for 1–40 years; and, OR, 2.1; 95%CI: 1.4–3.2 for > 40 years); this association was only weakly present in the first series; the odds ratio for uveal melanoma with birthplace in the south of the USA was 0.2 (95%CI: 0.0–0.7), which was statistically independent of the positive association between duration of residence in the south and uveal melanoma risk. Vajdic *et al.* (2001, 2002) found that the risk of choroid and ciliary body melanoma was increased in the highest categories of total sun exposure (OR, 1.6; 95%CI: 1.0–2.6), weekdays sun exposure (OR, 1.8; 95%CI: 1.1–2.8), and occupational sun exposure (OR, 1.7; 95%CI: 1.1–2.8); the underlying trends across quarters of exposure were reasonably consistent and statistically significant. These associations were largely due to stronger associations confined to men. Finally, the one cohort study (Håkansson *et al.*, 2001), based in the Swedish construction industry's health service, observed an increasing risk of ocular melanoma with increasing occupational sun exposure based on recorded job tasks (RR, 1.4; 95%CI: 0.7–3.0, for medium sun exposure; and, RR, 3.4; 95%CI: 1.1–10.5, for high sun exposure).

Five of the case–control studies limited their study to uveal melanoma (melanoma in the choroid, ciliary body, and iris), and one of these excluded iris melanoma because of small numbers. Two studies reported results for iris melanoma (Tucker *et al.*, 1985; Vajdic *et al.*, 2002). One study observed odds ratios of 3–5 for iris melanoma with the use of an eye shade when outdoors occasionally, rarely or never, relative to almost always (Tucker *et al.*, 1985), and the other observed an increased risk of iris melanoma in farmers (OR, 3.5; 95%CI: 1.2–8.9; Vajdic *et al.*, 2002). One study also reported results for conjunctival melanoma, but found no positive associations with measures of sun exposure (Vajdic *et al.*, 2002).

(c) *Meta-analyses*

Shah *et al.* (2005) and Weis *et al.* (2006) reported the results of meta-analyses of risk of ocular melanoma in relation to sun sensitivity characteristics and sun exposure, including both case–control and cohort studies (Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.10.pdf). A fixed-effects model was used except when statistically significant heterogeneity was found between the effects of individual studies and a random-effects model was used instead. A summary relative risk was reported only when four or more studies were included in the analysis. In the analysis by Shah *et al.* (2005), neither latitude of birth nor outside leisure was appreciably associated with ocular melanoma. There was weak evidence that occupational exposure to the sun increased ocular melanoma risk (RR for highest exposed category, 1.37; 95%CI: 0.96–1.96). [The Working group noted that this analysis did not include results of Lutz *et al.* (2005) or Schmidt-Pokrzywniak *et al.* (2009), but included those of Guénel *et al.* (2001), which are a component of Lutz *et al.* (2005). When the results of Lutz *et al.* (2005) are substituted for those of Guénel *et al.* (2001) and those of Schmidt-Pokrzywniak *et al.* (2009) added to the fixed effects meta-analysis, the meta-RR is 1.25 (95%CI: 1.02–1.54).]

The meta-analysis of Weis *et al.* (2006) provides strong evidence that having blue or grey eyes, fair skin and/or burning easily rather than tanning when exposed to the sun are associated with an increased risk of ocular melanoma. Hair colour was not associated with this cancer.

2.1.5 *Other sites*

Prompted at least in part by the hypotheses arising from ecological studies, case–control and cohort studies have been conducted in

which measures of personal exposure to solar radiation (loosely referred to here as sun or sunlight exposure) have been related to cancers in internal tissues (Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.11.pdf and Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.12.pdf). Studies that infer high sun exposure from a past history of skin cancer (basal cell carcinoma, squamous cell carcinoma or melanoma) were excluded (see for example, Tuohimaa *et al.*, 2007). It has been argued in respect of these studies that "the incidence of second cancers in individuals is elevated by several known and unknown mechanisms, including common etiological factors and predispositions, and influenced by possible biases in the ascertainment of second cancers […] The net direction of these influences will mostly be in the direction of elevated occurrence of second cancers, against which a possible effect of sunlight and vitamin D […] could be difficult to detect." (IARC, 2008). Thus, such studies are unlikely to be a reliable source of evidence for determining whether sun exposure causes or prevents any other cancers.

(a) Cancer of the colorectum

Two case–control studies have related estimates of individual sun exposure to risk of cancer of the colorectum. Based solely on death certificates, Freedman *et al.* (2002) observed a somewhat reduced risk (OR, 0.73; 95%CI: 0.71–0.74) with high ambient sunlight in the state of residence at the time of death, adjusted for age, sex, race, occupational sun exposure (inferred from usual occupation), physical activity, and socioeconomic status. In a large population-based study in which participants were interviewed, no appreciable association was found between cancer of the colon and sun exposure recalled for each season for the 2 years before case diagnosis. With the exception of the second quintile of exposure in women (OR, 1.3), the odds ratios for each quintile of exposure in each sex varied from 0.9–1.1, and were not significantly increased (Kampman *et al.*, 2000).

(b) Cancer of the breast

Three case–control and two cohort studies have examined the association between measures of sun exposure and breast cancer. In three studies reporting results for sun exposure assessed from location of residence, one found slightly higher risks in women residing in California (using 'south' as a reference; Laden *et al.*, 1997); the other two studies found reduced relative risks (0.73 and 0.74) with residence in areas of high mean daily solar radiation (John *et al.*, 1999; Freedman *et al.*, 2002), significantly so in one of these studies (Freedman *et al.*, 2002). Sun-related behaviour was recorded in three studies (John *et al.*, 1999; Freedman *et al.*, 2002; Knight *et al.*, 2007) and was inversely associated with risk for breast cancer for some measures. For example, the relative risks for breast cancer with frequent recreational and occupational sun exposure relative to rare or no exposure were 0.66 (95%CI: 0.44–0.99) and 0.64 (95%CI: 0.41, 0.98), respectively, in 5009 women from the NHANES Epidemiologic Follow-up Study (John *et al.*, 1999). For the highest category of estimated lifetime number of outdoor activity episodes at 10–19 years of age, the odds ratio was 0.65 (95%CI: 0.50–0.85) in a large Canadian case–control study (Knight *et al.*, 2007). In each study, these effect measures were adjusted for a measure of socioeconomic status and some other variables associated with breast cancer.

(c) Cancer of the ovary

In a case–control study, based on death certificates, the relative risk of cancer of the ovary was reduced in those residing in areas with high mean daily solar radiation (OR, 0.84; 95%CI: 0.81–0.88), but not in those with high occupational sun exposure (Freedman *et al.*, 2002).

(d) Cancer of the prostate

Four case–control studies (two hospital-based) and one cohort study (John *et al.*, 2004, 2007) examined the association between measures of sun exposure and risk for cancer of the prostate. In one case–control study conducted in two consecutive periods and with patients with benign prostatic hypertrophy as controls, the odds ratio for prostate cancer with highest lifetime sun exposure was [0.32 (95%CI: 0.20–0.51); combined odds ratio calculated from two reported odds ratios]. Odds ratios were similarly low with indirect measures of sun exposure, such as regular foreign holidays or childhood sunburn (Luscombe *et al.*, 2001; Bodiwala *et al.*, 2003). Two other studies showed weaker evidence of an inverse association of residence in a high solar radiation environment with cancer of the prostate (Freedman *et al.*, 2002; John *et al.*, 2004, 2007). Outdoor occupation, self-reported recreational sun exposure, physician-assessed sun exposure or actinic skin damage had no effect on prostate cancer risk in these studies. In a case–control study that included only cases of primary advanced cancer of the prostate (John *et al.*, 2005), a reduced risk for cancer of the prostate was reported with high values of sun exposure index (based on comparison of the measured reflectance of usually exposed and usually unexposed skin; OR, 0.51; 95%CI: 0.33–0.80), but with little evidence of similar associations with residential ambient solar radiation or total or occupational lifetime outdoor hours.

(e) Non-Hodgkin lymphoma and other lymphomas

While some early, mainly ecological studies, suggested that sun exposure might increase risk for non-Hodgkin lymphoma, studies of individual sun exposure suggest that recreational sun exposure may decrease its risk.

Two earlier studies in individuals assessed sunlight exposure based on place of residence, occupational title and, in one study, industry (Freedman *et al.*, 1997; Adami *et al.*, 1999). The results for residential exposure were conflicting: one study, in the USA, found a reduced relative risk with residence at lower latitudes (Freedman *et al.*, 1997); and the other, in Sweden, an increased risk (Adami *et al.*, 1999). They concurred, however, in finding reduced relative risks in people with high occupational sun exposure with values of 0.88 (95%CI: 0.81–0.96) in the USA and 0.92 (95%CI: 0.88–0.97; combined result for men and women) in Sweden. Subsequent studies focusing specifically on occupational sun exposure have not observed a reduced risk of non-Hodgkin lymphoma with higher exposure (van Wijngaarden & Savitz, 2001; Tavani *et al.*, 2006; Karipidis *et al.*, 2007). A study of non-Hodgkin lymphoma in children reported a reduced risk in those who had spent 15 or more days annually at seaside resorts, with an odds ratio of 0.60 (95%CI: 0.43–0.83; Petridou *et al.*, 2007).

All other studies (Hughes *et al.*, 2004; Smedby *et al.*, 2005; Hartge *et al.*, 2006; Soni *et al.*, 2007; Weihkopf *et al.*, 2007; Zhang *et al.*, 2007; Boffetta *et al.*, 2008; Kricker *et al.*, 2008) were included in a pooled analysis of original data from 8243 cases of non-Hodgkin lymphoma and 9697 controls in ten member studies of the InterLymph Consortium (Kricker *et al.*, 2008; Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-01-Table2.13.pdf). [The Working Group noted that results on sun exposure and non-Hodgkin lymphoma in three of these studies have not yet been published separately.] In eight studies in which a composite measure of total sun exposure (recreational plus non-recreational exposure) could be defined, the pooled odds ratio fell weakly with increasing sun exposure to 0.87 (95%CI: 0.71–1.05) in the fourth quarter of exposure. There was a steeper downtrend for recreational exposure to an odds ratio of 0.76 (95%CI: 0.63–0.91; *P* for trend, 0.005), and no appreciable downtrend for non-recreational exposure. Physical activity and obesity, which

might be confounding, were not controlled for in the analysis of any of the pooled studies.

Four case–control studies have reported on the association between sun exposure and Hodgkin lymphoma (Table 2.11 on-line); there was no consistent pattern of decreasing or increasing risk with different sun exposure measures (Smedby *et al.*, 2005; Petridou *et al.*, 2007; Weihkopf *et al.*, 2007; Grandin *et al.*, 2008). The same was true for multiple myeloma in two case–control studies (Boffetta *et al.*, 2008; Grandin *et al.*, 2008). One study found weak evidence of an increased risk of mycosis fungoides [a cutaneous lymphoma] in people with high occupational sun exposure [OR: 1.3 (95%CI: 1.0–1.9; combined result for men and women] (Morales-Suárez-Varela *et al.*, 2006).

2.2 Artificial UV radiation

2.2.1 Use of artificial tanning devices (sunlamps, sunbeds, solaria)

(a) Cutaneous melanoma, squamous cell carcinoma, and basal cell carcinoma

Two meta-analyses of skin cancer in relation to sunbed use have been undertaken over the past few years (Table 2.14). The first (IARC, 2006a, 2007a) was based on 19 informative published studies (18 case–control, of which nine population-based, and one cohort, all in light-skinned populations) that investigated the association between indoor tanning and skin cancers, and included some 7355 melanoma cases (Table 2.14). The characterization of the exposure was very varied across reports. The meta-relative risk for ever versus never use of indoor tanning facilities from the 19 studies was 1.15 (95%CI: 1.00–1.31); results were essentially unchanged when the analysis was restricted to the nine population-based case–control studies and the cohort study. A dose–response model was not considered because of the heterogeneity among the categories of duration and frequency of exposure used in the different studies. All studies that examined age at first exposure found an increased risk for melanoma when exposure started before approximately 30 years of age, with a summary relative risk estimate of 1.75 (95%CI: 1.35–2.26) (Table 2.14). The second meta-analysis (Hirst *et al.*, 2009) included an additional nested case–control study of melanoma (Han *et al.*, 2006), bringing the total number of melanoma cases to 7855, and the summary relative risk for melanoma in relation to ever versus never use of sunbeds was reported as 1.22 (95%CI: 1.07–1.39).

Regarding basal cell carcinoma and squamous cell carcinoma, a meta-analysis of the three studies on ever use of indoor tanning facilities versus never use showed an increased risk for squamous cell carcinoma of 2.25 (95%CI: 1.08–4.70) after adjustment for sun exposure or sun sensitivity (IARC, 2006a, 2007a). One study had information on age at first exposure of indoor tanning facilities and suggested that the risk increased by 20% (OR, 1.2; 95%CI: 0.9–1.6) with each decade younger at first use. The four studies on basal cell carcinoma did not support an association with the use of indoor tanning facilities (IARC, 2006a, 2007a).

(b) Ocular melanoma

Four case–control studies have reported explicitly on the association of artificial tanning devices and ocular melanoma (Tucker *et al.*, 1985; Seddon *et al.*, 1990; Vajdic *et al.*, 2004; Schmidt-Pokrzywniak *et al.*, 2009; Table 2.15). Odds ratios for the highest exposure categories in each were: 2.1 (95%CI: 0.3–17.9) (Tucker *et al.*, 1985); 3.4 (95%CI: 1.1–10.3) and 2.3 (95%CI: 1.2–4.3) for the population-based comparison and case–sibling comparison, respectively (Seddon *et al.*, 1990); 1.9 (95%CI: 0.8–4.3) (Vajdic *et al.*, 2004); and 1.3 to 2.1 depending on the control category (Schmidt-Pokrzywniak *et al.*, 2009). The only study to analyse dose–response found evidence of increasing risk with increasing duration of use (P = 0.04) and, less strongly, estimated

Table 2.14 Meta-analyses of use of artificial tanning devices and skin cancers

Reference, study location & period	Study description	Number of cases and controls	Exposure assessment	Exposure categories	Relative risk (95%CI)	Adjustment for potential confounders	Comments
IARC (2007a) Europe, north America and Australia 1971 to 2001	18 case–control studies (10 pop-based) and 1 cohort published in 1981–2005, with exposure assessment to indoor tanning	Cutaneous melanoma: 7355 cases and 11275 controls from case–control studies; cohort: 106379 members BCC-SCC (No. of cases not stated) from 5 case–control studies	All studies except two presented estimates for ever versus never	*Indoor tanning* Never use Ever use *Age first use* Never < 35 yr Never use Ever use Never use Ever use	**Melanoma** 1.0 1.15 (1.00–1.31) 1.0 1.75 (1.35–2.26) **BCC** 1.0 1.0 (0.6–1.9) **SCC** 1.0 2.25 (1.1–4.7)	All analyses adjusted for the maximum of potential confounders	One study presented results for men and women separately; Dose–response was not considered because of the heterogeneity among the categories of duration and frequency of exposure between studies.
Hirst *et al.* (2009) Europe, north America and Australia 1971 to 2002	18 case–control studies and 2 nested-cohort studies published in 1981–2006, with exposure assessment to indoor tanning	Cutaneous melanoma: 7885 cases and 24209 controls from all studies BCC/SCC: 1812 cases and 2493 controls from 6 case–control studies		*Indoor tanning* Never use Ever use Never use Ever use	**Melanoma** 1.0 1.22 (1.07–1.39) **BCC/SCC** 1.0 1.34 (1.05–1.70)		One study presented results for men and women separately; No summary risk estimate for BCC or SCC separately

BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

Table 2.15 Case–control studies of exposure to artificial tanning devices and ocular melanoma

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential cofounders	Comments
Tucker *et al.* (1985), USA, 1974–79	439 White patients with intraocular melanoma confirmed histologically or from highly reliable ancillary studies; participation rate, 89%	419 White patients with detached retina not due to tumours; matched by age, sex, race, date of diagnosis; participation rate, 85%	Telephone interview with detailed information about medical history, family history, employment, exposure to environmental agents, sunlight; details from ophthalmologic examination and medical history abstracted from medical records; interview with next-of-kin for 17% of cases and 14% of controls, half of them with spouses	*Sunlamp use* Never Rarely Occasionally Frequently	 1.0 1.3 (0.8–2.3) 1.3 (0.5–3.6) 2.1 (0.3–17.9)	Age, eye colour and history of cataract	
Seddon *et al.* (1990), Massachusetts, USA, 1984–87	White patients with clinically or histologically confirmed melanoma of the choroid, ciliary body or both, identified at local hospital or by mailing to ophthalmologists, diagnosed within previous yr; age range, 17–88 yr, mean, 57 yr; participation rate, 89% (see comments)	Series 1: selected by random digit dialing, matched 2:1 by sex, age, city of residence, 85% response rate Series 2: living sibling of cases, up to 4 siblings per case, median, 2; participation rate, 97%	Telephone interview including constitutional factors, ocular and medical histories, and exposure to environmental factors including natural and artificial sources of UV	**Case–control series 1*** *Sunlamp use* Never Rarely Occasionally or frequently **Case–control series 2*** *Sunlamp use* Never Rarely Occasionally or frequently	 1.0 0.7 (0.4–1.4) 3.4 (1.1–10.3) 1.0 0.9 (0.6–1.4) 2.3 (1.2–4.3)	Age, eye and skin colour, moles, ancestry, eye protection, outside work, fluorescent lighting, southern residence, yr of intense exposure	*Series 1: population-based, 197 cases and 385 controls; Series 2: not population-based, 337 cases and 800 sibling controls. 140 cases were included in both series.

Table 2.15 (continued)

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential cofounders	Comments
Vajdic *et al.* (2004), Australia, 1996–98	246 White Australian residents, aged 18–79 yr, with histopathologically or clinically diagnosed melanoma originating in the choroid, ciliary body; participation rate, 87% among those eligible	893 controls matched 3:1 by age, sex, residence, selected from electoral rolls; participation rate, 47%	Self-administered questionnaire, and telephone interview regarding sun exposure, sun-protective wear and quantitative exposure to welding equipment and sunlamps	*Sunlamp use**		Age, sex, place of birth, eye colour, ability to tan, squinting as a child and total personal sun exposure at 10, 20, 30 and 40 yr of age	*Sunlamps use includes use of sunbeds and tanning booths
				Never	1.0		
				Ever	1.7 (1.0–2.8)		
				Duration of use			
				≤ 1 mo	1.2 (0.5–2.8)		
				2 mo to 1 yr	1.8 (0.8–3.9)		
				> 1 yr	2.3 (0.9–5.6)		
				Lifetime hours of use			
				0.1–1.4	1.3 (0.5–3.2)		
				1.5–7.8	1.8 (0.8–4.2)		
				> 7.8	1.9 (0.8–4.3)		
				Period of first use			
				< 1980	1.4 (0.7–2.7)		
				1980–90	2.0 (0.8–4.7)		
				> 1990	4.3 (0.7–27.9)		
				Age at first use			
				> 20 yr	1.5 (0.8–2.6)		
				≤ 20 yr	2.4 (1.0–6.1)		
Schmidt-Pokrzywniak *et al.* (2009), Germany, 2002–05	459 cases of incident primary uveal melanoma diagnosed at 1 clinic, aged 20–74 yr	Control 1: 827 population-based, selected from mandatory list of residence, matched 2:1 on age (5-yr age groups), sex and region Control 2: 187 sibling controls, matched 1:1 by (+/– 10 yr) and sex when possible	Self-administered postal questionnaire and computer-assisted telephone interview	*Regular sunlamp use*			†Results presented for population controls. Odds ratios with sibling controls were somewhat higher, but with wider confidence intervals and not significant; *Sunlamps use includes use of sunbeds and tanning booths
				No	1.0		
				Yes	1.3 (0.9–1.8)		
				Age at first use			
				Never used	1.0		
				> 20 yr	1.3 (0.9–1.9)		
				< 20 yr	1.7 (0.8–3.6)		

yr, year or years

cumulative time of exposure (P = 0.06) (Vajdic *et al.*, 2004). The two most recent studies (Vajdic *et al.*, 2004; Schmidt-Pokrzywniak *et al.*, 2009) calculated odds ratios for exposure that started at or before 20 years of age and after this age; in both, the odds ratio was greater for exposure starting at the younger age. The results of Seddon *et al.* (1990) and Vajdic *et al.* (2004) were adjusted for sun sensitivity and personal sun exposure. [The Working Group noted that Schmidt-Pokrzywniak *et al.* (2009) found little evidence of associations between measures of personal sun exposure and ocular melanoma.]

(c) Internal cancers

Five case–control studies (Table 2.16) have reported on the association of the use of artificial tanning devices and cancer of the breast (one study), non-Hodgkin lymphoma (four studies), Hodgkin lymphoma (three studies), multiple myeloma (two studies), and lymphoproliferative syndrome (one study) (Smedby *et al.*, 2005; Hartge *et al.*, 2006; Knight *et al.*, 2007; Boffetta *et al.*, 2008; Grandin *et al.*, 2008). In all the studies of non-Hodgkin lymphoma, the risk was lower in people who had used artificial tanning devices than in those who had not; in two there was also a dose–response relationship across exposure categories with a P value for trend of ≤ 0.01 (Smedby *et al.*, 2005; Boffetta *et al.*, 2008). Odds ratios were also below unity for cancer of the breast (Knight *et al.*, 2007) and for Hodgkin lymphoma (Smedby *et al.*, 2005; Boffetta *et al.*, 2008), with a significant dose–response relationship (P value for trend = 0.004) in one study of Hodgkin lymphoma (Smedby *et al.*, 2005). Confounding with exposure to natural sunlight cannot be ruled out as an explanation for these inverse relationships because none of the studies adjusted the results for sun exposure.

2.2.2 Welding

Six separate case–control studies (seven reports) and one meta-analysis have reported on associations between welding and risk of ocular melanoma (Table 2.17). All studies reported an odds ratio for ocular melanoma above unity in most categories of exposure to welding. Seddon *et al.* (1990) reported on two sets of cases and controls and found an increased risk in only one of them. Lutz *et al.* (2005) found an increased risk with a "history of at least 6 months' employment in welding or sheet metal work," but not for "working with welding"; the increase observed was restricted to the French component of the study, which Guénel *et al.* (2001) had previously reported. The strongest associations of welding with ocular melanoma (although based on small numbers) were reported in those studies that restricted the exposure definition to "work as a welder," i.e. not including being in proximity to welding (Tucker *et al.*, 1985; Siemiatycki, 1991; Guénel *et al.*, 2001; Lutz *et al.*, 2005). Several studies showed evidence of dose–response relationships (Holly *et al.*, 1996; Guénel *et al.*, 2001; Vajdic *et al.*, 2004) with duration of employment or of use.

The meta-analysis (Shah *et al.*, 2005) estimated a meta-relative risk of 2.05 (95%CI: 1.20–3.51) for welding, using a random-effects model. [The Working Group noted that this study included results from Ajani *et al.* (1992), which overlap with those from case–control Series 1 of Seddon *et al.* (1990), and did not include those from the case–control Series 2 of Seddon *et al.* (1990). It also did not include results from Siemiatycki (1991).]

2.3 UVA, UVB, and UVC

Epidemiology has little capacity to distinguish between the carcinogenic effects of UVA, UVB, and UVC. UVC is not present in natural sunlight at the surface of the earth and is therefore not

relevant; in almost all circumstances humans are exposed simultaneously to UVB and UVA, and UVB and UVA exposures vary more or less in parallel (see Section 1). Several epidemiological approaches have been used in an attempt to distinguish the effects of UVA and UVB on skin cancer risk. Their major focus has been to assess whether solar UVA exposure contributes to the increased risk of cutaneous melanoma, for which there is some conflicting evidence in experimental studies (see Section 4). These include studies on exposure to UVA for artificial tanning, effect of sunscreens on melanoma risk, and UVB phototherapy without associated exposure to PUVA (psoralen-UVA photochemotherapy).

PUVA is the combination of psoralen with UVA radiation, and is used in the treatment of psoriasis. PUVA has been reviewed previously by two IARC Working Groups and there is *sufficient evidence* that PUVA therapy is *carcinogenic to humans (Group 1*), causing cutaneous squamous cell carcinoma (IARC, 1986, 2012), and these studies will not be reviewed here.

2.3.1 Descriptive studies

Garland *et al.* (1993) noted that "rising trends in the incidence of and mortality from melanoma have continued since the 1970s and 1980s, when sunscreens with high sun protection factors became widely used." They related this observation to the fact that commonly used chemical sunscreens had blocked UVB but not UVA; and the possibility that by preventing erythema, sunscreens would permit extended sun exposure and thus substantially increase exposure to UVA. However, nearly half of the melanoma mortality increase between 1950–54 and 1990–94 in the USA in white men and more than half of that in white women had occurred by 1970–74, with only a minor upward perturbation in the trend after 1970–74. Thus, there probably was not a close association between increasing use of sunscreens blocking UVB and the increasing risk of melanoma.

Moan *et al.* (1999) plotted the relationships of UVB and UVA irradiances and incidence rates of cutaneous basal cell carcinoma, squamous cell carcinoma and melanoma using data from Australia, Canada, the Czech Republic, Denmark, Finland, Iceland, Norway, New Zealand, Sweden, Scotland, USA, and the United Kingdom. As expected, all were inversely related to latitude but the slope of the fitted linear relationship was numerically smaller for UVA than for UVB, and for melanoma than for basal cell carcinoma and squamous cell carcinoma. Estimates of biological amplification factors (relative increase in risk per unit increase in exposure) based on these slopes for UVB were, in men and women respectively, 2.8 and 2.8 for basal cell carcinoma, 3.1 and 2.9 for squamous cell carcinoma, and 1.3 and 1.0 for melanoma. Those for UVA and melanoma were 3.8 and 2.9, respectively, suggesting that UVA may play a significant role in the induction of melanomas.

2.3.2 Exposure to artificial UVA for tanning purposes

Early artificial tanning devices emitted both UVB and UVA. UVB emissions were subsequently reduced relative to UVA, presumably to reduce skin cancer risk, but have been increased again recently to mimick the sun and to produce longer lasting tans (see Section 1). In principle these periods of different relative exposures to UVA and UVB during artificial tanning could be used to evaluate the relative effects of UVA and UVB on skin cancer risk. Veierød *et al.* (2003, 2004) attempted this analysis in a cohort study of Norwegian and Swedish women who had reported their use of a sunbed or sunlamp (solarium) in different age periods on entry to the cohort. They defined three subgroups of women: those who had used solaria in the period 1963–83 (mainly before they became mainly

Table 2.16 Associations of use of artificial tanning devices with cancers of internal tissues[a]

Reference, study location and period	Cancer type	Exposure assessment	Exposure categories	Relative risk
Knight *et al.* (2007), Canada, 2003–04	Breast cancer	Telephone interview	**Ever sunlamp use**	
			Age 10–19	
			No	1.0
			Yes	0.81 (0.57–1.14)
			Age 20–29	
			No	1.0
			Yes	0.88 (0.66–1.18)
			Age 45–54	
			No	1.0
			Yes	0.84 (0.64–1.11)
Hartge *et al.* (2006), USA, 1998–2000	Non-Hodgkin lymphoma	Self-administered questionnaire and computer assisted personal interview	*Use of sunlamp or tanning booth*	
			Never	1.0
			Ever	0.88 (0.66–1.19)
			Only after age 20	0.97 (0.69–1.37)
			Before age 20	0.72 (0.45–1.14)
			< 5 times	0.78 (0.46–1.32)
			5–9 times	0.90(0.52–1.58)
			10+ times	0.90 (0.61–1.30)
Smedby *et al.* (2005), Denmark and Sweden, 1999–2002	Non-Hodgkin lymphoma	Computer assisted telephone interview	*Solaria/sun lamp use*	
			Never	1.0
			< 10 times	1.0 (0.9–1.2)
			10–49 times	0.9 (0.8–1.0)
			50 times or more	0.8 (0.7–1.0)
	Hodgkin lymphoma		Never	1.0
			< 10 times	0.8 (0.6–1.0)
			10–49 times	0.7 (0.5–0.9)
			50 times or more	0.7 (0.5–0.9)

Table 2.16 (continued)

Reference, study location and period	Cancer type	Exposure assessment	Exposure categories	Relative risk
Boffetta *et al.* (2008), France, Germany, Ireland, Italy, and Spain, 1998–2004	Non-Hodgkin lymphoma	Interviewer administered questionnaire	*Sunlamp use*	
			Never	1.0
			1–24 times	0.79 (0.59–1.04)
			25 times or more	0.69 (0.51–0.93)
	Hodgkin lymphoma		Never	1.0
			1–24 times	0.86 (0.53–1.39)
			25 times or more	0.93 (0.57–1.50)
	Multiple myeloma		Never	1.0
			1–24 times	0.76 (0.41–1.41)
			25 times or more	1.10 (0.59–2.05)
Grandin *et al.* (2008), France, 2000–04	Non-Hodgkin lymphoma	Self and interviewer administered questionnaires	*Aesthetic use of artificial UV radiation*	
			No	1.0
			Yes	1.1 (0.7–1.7)
			Regularly	0.5 (0.2–1.3)
			Occasionally	1.4 (0.8–2.3)
	Hodgkin lymphoma		No	1.0
			Yes	1.6 (0.7–3.6)
			Regularly	0.6 (0.1–3.3)
			Occasionally	2.2 (0.9–5.5)
	Lymphoproliferative syndrome		No	1.0
			Yes	1.5 (0.7–3.5)
			Regularly	0.9 (0.2–4.6)
			Occasionally	1.9 (0.7–4.7)
	Multiple myeloma		No	1.0
			Yes	1.2 (0.4–3.6)
			Regularly	0.8 (0.1–7.3)
			Occasionally	1.4 (0.4–4.9)

[a] In none of these studies was potential confounding with exposure to natural sunlight controlled in the analysis

yr, year or years

Table 2.17 Case–control studies on welding and ocular melanoma

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk	Adjustment for potential confounders	Comments
Tucker *et al.* (1985), USA, 1974–79	439 White patients with intraocular melanoma confirmed histologically or from highly reliable ancillary studies; participation rate, 89%	419 White patients with detached retina not due to tumours; matched by age, sex, race, date of diagnosis; participation rate, 85%	Telephone interview with detailed information about medical history, family history, employment, exposure to environmental agents, sunlight; details from ophthalmologic examination and medical history abstracted from medical records; interview with next-of-kin for 17% of cases and 14% of controls, half of them with spouses	*Ever worked as a welder* No Yes	 1.0 10.9 (2.1–56.5)	Age, eye colour and history of cataract	
Seddon *et al.* (1990), Massachusetts, USA, 1984–87	White patients with clinically or histologically confirmed melanoma of the choroid, ciliary body or both, identified at local hospital or by mailing to ophthalmologists, diagnosed within previous yr; age range, 17–88 yr, mean, 57 yr; participation rate, 89% (see comments)	Series 1: selected by random digit dialing, matched 2:1 by sex, age, city of residence, 85% response rate Series 2: living sibling of cases, up to 4 siblings per case, median, 2; participation rate, 97%	Telephone interview including constitutional factors, ocular and medical histories, and exposure to environmental factors including natural and artificial sources of UV	**Case–control series 1** *Exposure to welding arc* No Yes **Case–control series 2** *Exposure to welding arc* No Yes	 1.0 1.3 (0.5–3.1) 1.0 0.9 (0.6–1.5)	Age, eye and skin colour, moles, ancestry, use of sunlamps, eye protection, outside work, fluorescent lighting, southern residence, yr of intense exposure	Series 1: population-based, 197 cases and 385 controls Series 2: not population-based, 337 cases and 800 sibling controls. 140 cases were included in both series. Result for case series 1 also was reported by Ajani *et al.* (1992) using the same numbers but with fewer covariates in the logistic regression model (see below).

Table 2.17 (continued)

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk	Adjustment for potential confounders	Comments
Siemiatycki (1991), Montreal, Canada, 1979–85	[33] incident male cases of uveal melanoma, aged 35–70 yr, histologically confirmed; response rate, 69.6%	533 population controls; participation rate, 72%	Personal interview and collection of detailed occupational history	*Occupational exposure to arc welding fumes* No Yes	 1.0 8.3 (2.5–27.1)	Age, family income, ethnicity, respondent type, cigarette and alcohol indexes	4 exposed cases
Ajani *et al.* (1992), USA, 1984–87	197 White patients with uveal melanoma, histologically confirmed, diagnosed during the previous yr, residents of 6 New England States; mean age, 59.2 yr, range 18–88 yr; participation rate, 92%	385 controls selected by random digit dialling, matched 2:1 for age (+/– 8 yr), sex, telephone exchange; mean age, 58.3 yr, range 19–88 yr; response rate, 85%	Telephone interview with occupational history and exposures related to work occurring 15 yr before the interview.	*Exposure to welding arc* No Yes	 1.0 0.99 (0.48–2.05)	Age, ancestry, skin colour, moles, use of sunlamps, past income level	Same population as in study by Seddon *et al.* (1990) in case series 1 using the same numbers but with more covariates in the logistic regression model (see above).
Holly *et al.* (1996), USA, 1978–87	221 male White patients with histologically confirmed uveal melanoma, age 20–74 yr residing in 11 States; participation rate, 93%	447 controls selected by random digit dialling, matched 2:1 by age (5-yr age group) and residential area; interview rate, 77%	Interviewer administered questionnaire with demographic and phenotypic caracteristics, occupational history, exposure to chemicals.	*Welding** No Yes *Years from start of occupation to diagnosis or interview* ≤ 10 11–29 ≥ 30	1.0 2.2 (1.3–3.5) 1.2 (0.2–6.6) 1.5 (0.7–3.0) 2.1 (1.1–4.0)	Age, number of large nevi, eye colour, tanning or burning response to 30 min. sun exposure in the summer noond sun	* Self welding or in proximity to others for > 3 h a wk for > 6 mo

Table 2.17 (continued)

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk	Adjustment for potential confounders	Comments
Guénel *et al.* (2001), France 1995–96	50 cases (29 men and 21 women) identified from records of local pathology departments for surgery, and from 2 cancer treatment centres in France; diagnosis confirmed by pathologists or ophthalomogic report; participation rate, 100%	479 (321 men, 158 women) controls selected from electoral rolls, frequency matched by age (5-yr interval), sex and study area; participation rate, 76%	Face-to-face interview, or occasionally telephone interview	*Worked for six mo or more as a welder or sheet metal worker* No Yes *Duration of employment as a welder* Less than 20 yr 20 yr or more	 1.0 7.3 (2.6–20.1) 5.7 (1.6–19.8) 11.5 (2.4–55.5)	Age	Data also included in analysis of Lutz *et al.* (2005). Results shown here for men only; only one woman in this study had worked as a welder and she was a case.
Vajdic *et al.* (2004), Australia, 1996–98	246 White Australian residents, aged 18–79 yr, with histopathologically or clinically diagnosed melanoma originating in the choroid, ciliary body; participation rate, 87% among those eligible	893 controls matched 3:1 by age, sex, residence, selected from electoral rolls; participation rate, 47%	Self-administered questionnaire, and telephone interview regarding sun exposure, sun-protective wear and quantitative exposure to welding equipment and sunlamps	*Own welding* Never Ever *Duration of use* 0.1–4.0 yr 4.1 to 22.0 yr > 22 yr *Lifetime hours of use* 0.1–52.0 52.1–858.0 > 858 *Age at first use* > 20 yr ≤ 20 yr	 1.0 1.2 (0.8–1.7) 0.8 (0.4–1.4) 1.2 (0.7–2.2) 1.7 (1.0–2.7) 1.1 (0.6–1.9) 1.4 (0.8–2.3) 1.1 (0.6–1.9) 1.2 (0.8–1.9) 1.2 (0.7–1.9)	Age, sex, place of birth, eye colour, ability to tan, squinting as a child and total personal sun exposure at 10, 20, 30, and 40 yr of age	

Table 2.17 (continued)

Reference, study location and period	Cases	Controls	Exposure assessment	Exposure categories	Relative risk	Adjustment for potential confounders	Comments
Lutz *et al.* (2005), Denmark, Latvia, France, Germany, Italy, Sweden, Portugal, Spain, and the United Kingdom, 1995–96	292 incident cases of uveal melanoma, identified from ophthalmologic departments, hospital records or cancer registries aged 35–69 yr; participation rate, 91%	2062 population controls selected from population registers, electoral rolls or practitioner, frequency matched by region, sex and 5-yr birth cohorts; participation rate, 61%; 1094 cancer controls randomly selected from colon cancer patients; participation rate, 86%	Questionnaire with face-to-face or telephone interview	*Worked for six mo or more as a welder or sheet metal worker* No Yes *Working with welding* No Yes	 1.0 2.2 (1.2–4.0) 1.0 0.9 (0.6–1.5)		Data from France reported in analysis of Guénel *et al.* (2001). Results shown here for men only; only one woman in this study had worked as a welder and was a case.

d, day or days; h, hour or hours; min, minute or minutes; mo, month or months; wk, week or weeks; yr, year or years

UVA-emitting), the period 1979–91 (mainly after solaria were designed to emit mainly UVA) or the period 1975–87 (covering both categories of solarium) when they were 20–29 years of age. The odds ratios for solarium use in these subgroups were 3.75 (95%CI: 1.73–8.13) for use in 1963–83, 3.19 (95%CI: 1.22–8.32) for use in 1979–91, and 1.28 (95%CI: 0.46–3.60) for use in 1975–87. These results show little difference between those exposed in the earlier and later periods of solarium use. [The Working Group noted that only seven cases of melanoma were observed in each of these periods, and there was little statistical power to see a difference.] A recent meta-analysis of use of artificial tanning devices and skin cancer (IARC, 2007b) reported that the relative risks of melanoma associated with ever use of a sunbed or sunlamp did not vary with year of publication of a study or the first year of a study period, where available. [The Working Group noted that the most relevant time metric would be year of first reported use of a sunbed or sunlamp, rather than the year of publication or first year of study period.]

2.3.3 Use of sunscreens and risk for melanoma

Initially, sunscreens contained only UVB absorbers; more recently they have covered a broader spectrum with the addition of UVA reflectors or absorbers, although many are still less effective against the higher wavelengths of UVA than they are against UVB (see Section 1). Recent meta-analyses of published observational studies of sunscreen and melanoma, each including slightly different subsets of studies, have found meta-relative risks close to unity with highly significant heterogeneity among studies: 1.11 (95%CI: 0.37–3.32) with a *P* value for heterogeneity < 0.001 (Huncharek & Kupelnick, 2002); 1.0 (95%CI: 0.8–1.2) with a *P* value for heterogeneity < 0.001 (Dennis *et al.*, 2003); and 1.2 (95%CI: 0.9–1.6) with a *P* value for heterogeneity < 0.0001 (Gorham *et al.*, 2007). [The Working Group noted that although these observations might be explained by a lack of effectiveness of early sunscreens against higher wavelengths of UVA, there are other possible, and probably more plausible, explanations. First, there is undoubted positive confounding between sunscreen use and sun exposure, and probably also sun sensitivity. Although this confounding can, in principle, be dealt with by adjustment for sun exposure and sun sensitivity in multiple variable models of the association of sunscreen use with melanoma risk, inaccurate measurement of these confounders limits the ability of modelling to control their confounding. Thus, residual confounding could easily explain the lack of protective effect of sunscreens seen in observational studies of melanoma (IARC, 2001). Second, there is clear evidence of adaptation to the use of sunscreens such that people who apply sunscreens before outdoor recreation may increase their duration of exposure to the sun (Autier *et al.*, 2007) so that their dose of erythemal UV radiation may not change. Thus, observed associations of sunscreens with risk of melanoma (or other skin cancers) in observational studies do not provide useful information regarding the relative effects of UVB and UVA on cancer risk.]

2.3.4 UVB phototherapy

UVB phototherapy is used to treat a variety of skin conditions. Lee *et al.* (2005) reviewed the literature and concluded that there was no evidence of an increased risk of skin cancer in those who had received UVB phototherapy as their only form of UV phototherapy. [The Working Group noted that only three cases of melanoma were identified among about 1000 who had received this therapy.]

Lim & Stern (2005) extended follow-up of 1380 patients with severe psoriasis who had been treated with variations of PUVA, methotrexate, UVB, topical tar, and ionizing radiation. In

patients who had less than 100 PUVA treatments, the incidence rate ratio for cutaneous squamous cell carcinoma with ≥ 300 UVB treatments was 0.81 (95%CI: 0.34–1.93) for chronically sun-exposed sites, and 2.75 (95%CI: 1.11–6.84) for rarely to intermittently sun-exposed sites. The corresponding values for basal cell carcinoma were 1.38 (95%CI: 0.80–2.39) for chronically sun-exposed sites and 3.00 (95%CI: 1.30–6.91) for intermittently sun-exposed sites. [The Working Group noted that the possibility that the observed effect required interaction with PUVA or another treatment for psoriasis cannot be ruled out in this study.] Hearn *et al.* (2008) described the results of follow-up of 3867 patients who had received narrow-band UVB phototherapy, a quarter of whom had also received PUVA. In comparison with data from the Scottish Cancer Registry, there were near 2-fold increases in the risk of first squamous cell carcinoma [two observed cases] and of first basal cell carcinoma [14 observed cases] for treatment with narrow-band UVB only, but their 95% confidence intervals included unity. For melanoma, the relative risk was just below 1. For those who had more than 100 UVB therapy treatments, the risks, relative to those who received 25 or less such treatments, were 1.22 (95%CI: 0.28–4.25) for basal cell carcinoma, 2.04 (95%CI: 0.17–17.8) for squamous cell carcinoma, and 1.02 (95%CI: 0.02–12.7) for melanoma. Two previous small studies of narrow-band UVB, of 126 (Weischer *et al.*, 2004) and 484 patients (Black & Gavin, 2006), observed only one skin cancer between them, an in-situ melanoma, in less than 10 years of follow-up.

Given the few cases of skin cancer so far reported in patients given UVB phototherapy as their only form of phototherapy, the statistical power of currently available studies to detect other than a large increase in relative risk of any type of skin cancer with this therapy, and, therefore, of UVB specifically is weak.

2.4 Synthesis

2.4.1 Solar radiation

In Caucasian populations, both basal cell carcinoma and squamous cell carcinoma are strongly associated with solar radiation, as measured by indicators of accumulated solar skin damage (e.g. increasing age, especially for squamous cell carcinoma; and presence of actinic keratoses), and secondarily by recalled episodes of acute solar skin damage (multiple sunburns).

The causal association of cutaneous melanoma and solar exposure is established, this link has become clearer in the last decade or so through the observation of the site-specific heterogeneity of melanoma, the lower-than-average phenotypic risk for skin carcinogenesis among outdoor workers, and the recognition that the different associations of melanoma with sun exposure observed among Caucasian people at different latitudes around the world correlate with marked variations in sun exposure opportunity and behaviour.

Five case–control studies of cancer of the lip have been published. The three earliest studies found apparent increases in risk with outdoor work, but use of tobacco could not be ruled out as an explanation for these associations. The two later studies both took account of possible confounding of outdoor exposure with tobacco smoke. One of them, in women, showed increased risks for cancer of the lip with several measures of exposure, together with strong and moderately consistent dose–response relationships. The other, in men, found no increase in risk with leisure time or holiday sun exposure but a substantial increase in risk with cumulative exposure during outdoor work during the summer months, without any indication of dose–response across four categories. This lack of dose–response suggests bias rather than a causal effect.

Four case–control studies reported at least one result each suggesting that sun exposure is associated with conjunctival intraepithelial neoplasia or squamous cell carcinoma of the eye. Only one study was exclusively of conjunctival squamous cell carcinoma; in this study and another, the relevant exposure variables (office work and cultivating the fields) were only indirect measures of sun exposure. A very large difference between cases and controls in prevalence of conjunctival solar elastosis in another study raised concerns about possible bias. The remaining study reported a strong association of ocular surface dysplasia with solar keratoses and increasing risk with increasing duration of residence at ≤ 30° south latitude. However, only 22% of its cases had conjunctival squamous cell carcinoma.

Two out of three studies that examined the distribution of choroidal melanomas found them to be concentrated in the central area or the macula area of the choroid, which coincides with the estimated distribution of light in the retinal sphere. Of ten case–control studies of ocular melanoma published from 1985 to 2009, four reported statistically significant associations of one or more measures of sun exposure with ocular melanoma. In two studies, these associations were with the latitude of birth or of residence in early life, with some inconsistency between them. In the other two, which were more recent and had better measures of exposure than many previous studies, one study related only to occupational sun exposure and showed a strong association with a dose–response relationship, and the strongest association seen in the other was with occupational sun exposure and showed evidence of a dose–response relationship. These results relate principally to choroid and ciliary body melanomas (the dominant types). Two studies reported results consistent with a positive association of small numbers of iris melanomas with sun exposure. One study with a small number of conjunctival melanomas found no such association.

The associations of sun exposure with several internal cancers have been investigated in case–control and cohort studies, generally with the hypothesis that sun exposure might be protective against such cancers. The cancers investigated included cancer of the colorectum (two studies), of the breast (five studies), of the ovary (one study), of the prostate (four studies), and several cancers of the lymphatic tissue, principally non-Hodgkin lymphoma and Hodgkin disease (15 studies). Exposure metrics used in these studies included residential or occupational ambient solar radiation, recreational or non-recreational sun exposure, recent and lifetime sun exposure, and sun-related behaviour. The results were mostly inconsistent.

2.4.2 Artificial sources of UV

(a) Tanning appliances

Two meta-analyses investigated the association between indoor tanning and skin cancers.

The summary relative risk for ever versus never use of indoor tanning facilities was significantly increased for melanoma, with no consistent evidence for a dose–response relationship. All studies that examined age at first exposure found an increased risk for melanoma when exposure started before approximately 30 years of age, with a summary relative risk estimate of 1.75.

For squamous cell carcinoma, the three available studies found some evidence for an increased risk, especially when age at first use was below 20 years. Studies on basal cell carcinoma did not support an association with use of indoor tanning facilities.

Four case–control studies reported on associations between artificial tanning devices and ocular melanoma. Each observed an increase in risk of ocular melanoma in the highest category of exposure to these devices, and there were

indications of a dose–response relationship in three of the studies. In two studies, the risk was higher in people who began exposure before 20 years of age than those who began after this age. Possible confounding with natural sun exposure was explicitly addressed in two of the studies.

Five studies reported on the association of use of indoor tanning devices with internal cancers, specifically breast cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, and multiple myeloma. Most studies found little evidence of an association. Two studies observed inverse associations between the use of internal tanning devices and non-Hodgkin lymphoma, and one study with Hodgkin lymphoma. Possible confounding with exposure to natural sunlight cannot be ruled out in any of these studies.

(b) Welding

Six case–control studies reported on the association between welding and ocular melanoma. All found evidence of a positive association, which was strong in three studies, each of which related specifically to working as a welder or sheet metal worker (other studies included working in proximity to welding in the definition of exposure). In each of three studies in which it was examined, there was evidence of a dose–response relationship.

2.4.3 UVA, UVB, UVC

Several sources of evidence were examined to see if the carcinogenic effects of UVA and UVB could be distinguished: descriptive studies of skin cancer have shown that the slope of latitude variation in incidence of melanoma is less than that in incidence of squamous cell carcinoma and basal cell carcinoma, suggesting that melanoma incidence is more influenced by UVA irradiance than are squamous cell carcinoma and basal cell carcinoma. Present data on the risk for melanoma associated with the of UV-emitting tanning devices show little evidence that it varies with the relative contributions of UVB and UVA emitted from the devices. There is little or no evidence to suggest that the use of sunscreens that block mainly UVB radiation increased the risk for melanoma. Studies of patients exposed exclusively to UVB phototherapy show weak evidence of an increase in risk of squamous cell carcinoma and basal cell carcinoma, based on a few cases.

3. Cancer in Experimental Animals

The previous *IARC Monograph* on solar and ultraviolet radiation concluded that there was *sufficient evidence* for the carcinogenicity of solar radiation, broad-spectrum ultraviolet radiation, ultraviolet A, ultraviolet B and ultraviolet C radiation in experimental animals (IARC, 1992).

The experimental induction of skin cancers in mice following exposure to a mercury-arc lamp was first reported by Findlay (1928). Initially, haired albino mice were used, but hairless Skh-1 (albino) and Skh-2 (pigmented) immunocompetent mice and eventually immunodeficient nude mice or transgenic mice are now used.

Hundreds of studies have clearly established the carcinogenic activity of UVR in mice. The action spectrum for ultraviolet-induced skin carcinogenesis in albino hairless mice has been determined and shows a peak in the UVB range (280–315 nm) and a steep decrease in the UVA range (315–400 nm). However, while the induction of non-melanoma skin cancer is regularly obtained in mice, the induction of melanoma was exceptional.

Solar radiation was tested for carcinogenicity in a series of studies in mice and rats. Large numbers of animals were studied (600 rats and 2000 rats and mice), and incidences of squamous-cell carcinoma of the skin and of the conjunctiva were clearly increased in most of the surviving mice and rats (Roffo, 1934, 1939; IARC, 1992).

Broad-spectrum UVR (solar-simulated radiation and ultraviolet lamps emitting in the entire UV wavelength range) was tested for carcinogenicity in two large studies in mice (Grady *et al.*, 1943; Blum, 1959; IARC, 1992), several studies in rats, and one study in hamsters and guinea-pigs (Freeman & Knox, 1964; IARC, 1992). Incidences of squamous-cell carcinoma of the skin and of the cornea/conjunctiva were clearly increased in rats and mice. Hamsters developed malignant tumours of the cornea. No eye tumours were observed in guinea-pigs.

In several studies in mice exposed to sources emitting mainly UVA radiation, squamous-cell carcinomas of the skin were clearly induced. Both short-wavelength UVA (UVA2, 315–340 nm) and long-wavelength UVA (UVA1, 340–400 nm) were effective (IARC, 1992).

In several studies in mice exposed to sources emitting mainly UVB radiation, the predominant tumour type was squamous-cell carcinoma of the skin. Skin papillomas were observed in one study in rats and one study in hamsters. Invasive melanomas were induced in two experiments in platyfish-swordtail hybrid fish. In two out of three studies in opossums (*Monodelphis domestica*), squamous-cell carcinomas were shown to develop; in one of these three studies, malignant tumours of the cornea were observed and melanocytic neoplasms of the skin were reported in another one (IARC, 1992).

In some studies in mice exposed to sources emitting mainly UVC radiation, squamous-cell carcinomas of the skin were clearly induced. In one study in rats, keratoacanthomas of the skin were observed. In none of the experiments involving UVC was it possible to exclude completely a contribution of UVB, but the size of the effects observed indicate that they cannot be due to UVB alone (IARC, 1992).

UVR has been studied in protocols involving two-stage chemical carcinogenesis. UVR has been reported to exert many effects on the carcinogenic process, including initiation, promotion, cocarcinogenicity and even tumour inhibition. Chemical immunosuppressive agents have been shown to enhance the probability of developing UVR-induced tumours in mice (IARC, 1992).

Studies released since the previous *Monograph* are summarized below.

3.1 Non-melanoma skin cancer

See Table 3.1

3.1.1 Mouse

Most of the recent studies were not designed to test whether or not the radiation used was carcinogenic per se but to investigate the process of UV carcinogenesis, or to test enhancement or inhibition of photocarcinogenicity by drugs and chemical agents. Methods for testing photocarcinogenicity have been standardized to meet the requirements of regulatory agencies (Forbes *et al.*, 2003; Sambuco *et al.*, 2003).

Recent studies have mainly focused on the mechanisms of UV-induced carcinogenesis and have used specific strains of mice. Sencar mice were derived by selective breeding for susceptibility to chemical carcinogens. They are more sensitive th an other mouse strains to a variety of chemical initiators and promoters (e.g. 7,12-dimethylbenz(a)anthracene (DMBA) and 12-*o*-tetradecanoylphorbol-13-acetate (TPA)) as well as to UV radiation. Sencar mice have been widely used to study multistage skin carcinogenesis. Using these mice, squamous cell carcinomas (SCCs) and malignant spindle cell tumours (SCTs) appeared within 16-18 weeks and 30 weeks of irradiation respectively (Tong *et al.*, 1997, 1998). Tong *et al.* (1997, 1998) have also shown that alterations in the *Tp53* gene are frequent events in SCCs induced by chronic UV exposure in Sencar mouse skin, and that overexpression of H-Ras-p21 in conjunction with aberrant expression of keratine K13 is a frequent event in UVR-induced SCCs in Sencar mouse

Table 3.1 Non-melanoma skin cancers induced in mice and opossum exposed to ultraviolet radiation

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, Sencar (F) up to 60 wk Tong *et al.* (1997, 1998)	63, 10 controls exposed to UVR from Dermalight 2001 sun lamp (3 ×/wk, 8 min each time, for 18 wk). Total UVB dose = 139.2 J/m^2 UVR-induced skin tumours biopsied when 1.5 × 1.5 mm for histological examination, immunohistochemical detection of p53, Hras-p21 and keratin K13 expression, and DNA isolation. Skin biopsies from untreated control mice.	Among all 73 tumours biopsied: 4% papillomas, 54% SCCs, 36% spindle cell tumours (SCT), 6% dermal fibromas and BCCs. *Tp53* mutations (exon 5) in 10/37 (27%) of SCCs and 12/24 (50%) of SCTs Hras-p21 expressed in 24/36 (67%) of SCCs but not in normal skin SCTs or UV-exposed skin. Co-expression with K13 in 47% SCCs.	SCCs begin to appear 18 wk after initiation of UV irradiation. Among the 8 mutations, 3/8 (38%) were C → T changes (codons 146 and 158)-a typical "UV-signature" mutation-and 3/8 (38%) were C → A changes (codons 150 and 193), which is also a frequent mutation pattern induced by UVR.
Mice, Tg.AC (F) 20 wk Trempus *et al.* (1998)	10 animals/group 3 exposures (every other d) on shaved back 2.6 to 43.6 kJ/m^2 (cumulative). FS40T12 sunlamp (60% UVB, 40% UVA, total output 1.6 mW/cm^2)	Papillomas develop from 4 wk in a dose dependent manner, that progress to malignancy in the high UV exposure groups: - 21.8 kJ/m^2: 6/10 (60%) mice with SCC or SCT at 23–30 wk - 43.6 kJ/m^2: 5/9 (55%) mice with SCC or SCT at 18–30 wk	UV-induced tumours harbour few *Tp53* mutations. In contrast, UV-exposed skin show *Tp53* activation in the basal layer.
Mice, PKCε transgenic FVN/B starins 215, 224 sex and duration (NR) Wheeler *et al.* (2004, 2005)	number/group at start (NR) exposed to UVR (2 kJ/m^2) from a bank of 6 Kodacell filtered FS40 sunlamps, 3 ×/wk, up to 38 wk.	SCC develop earlier and more frequently in transgenic mice than in normal littermates. Up to 60% mice developed SCC by 38 wk.	PKCε overexpression sensitizes skin to UVR-induced cutaneous damage and development of squamous cell carcinoma possibly at the promotion step of carcinogenesis, and this is probably accomplished by promoting the enhanced induction and release of specific cytokines such as TNFα.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, Skh-1 (F) 26 wk Rossman *et al.* (2002)	15 animals/group 1.7 kJ/m^2 solar UVR (mostly UVB) 3 ×/wk, ± 10 mg/L sodium arsenite in drinking-water for 26 wk	2.4-fold increase in yield of tumours in mice given arsenite compared with mice given UVR alone. Tumors (mostly SCCs) appeared only in UVR treated mice, and only on the exposed area (backs) of the mice.	Low (non toxic) concentrations of arsenite can enhance the onset and growth of malignant skin tumours induced by a low (non erythemic) dose of UVR in mice. Tumors occurring in mice given UVR plus arsenite appeared earlier (time to first tumour < 60 d *vs* > 80 d after UVR exposure alone) and were much larger than in mice given UVR alone.
Mice, Skh-1 (F) 182 d Burns *et al.* (2004)	Number at start (NR) Mice were fed sodium arsenite continuously in drinking-water starting at 21 d of age at concentrations of 0.0, 1.25, 2.5, 5.0, and 10 mg/L. At 42 d of age, solar spectrum UVR exposures were applied every other d (3 ×/wk) to the dorsal skin at 1.0 kJ/m^2 per exposure until the experiment ended at 182 d.	More than 95% of the tumours were SCCs. Only UVR irradiated mice developed locally invasive SCCs. Mice exposed only to UVR: 2.4 ± 0.5 cancers/mouse at 182 d. Arsenite enhanced the UVR-induced cancer yield in a linear pattern up to a peak of 11.1 ± 1.0 cancers/mouse at 5.0 mg/L arsenite (i.e. peak enhancement ratio: 4.63 ± 1.05). A decline occurred to 6.8 ± 0.8 cancers/mouse at 10.0 mg/L arsenite.	This study was designed to establish dose–response relationship for cancer enhancement in a new mouse skin model using arsenite in drinking-water in combination with chronic topical UVR exposures Arsenite alone and UVR alone induced epidermal hyperplasia, but the combined exposures have a greater than additive effect. 50% cancer incidence occurred at 140 d in the UVR only group, whereas in the highest response group (UVR plus 5.0 mg/L), 50% incidence occurred at 109 d.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, SK1-hrBD (F) 6 mo Uddin *et al.* (2005)	15-30 animals/group Weanling mice were exposed to solar spectrum UVR alone (1 kJ/m^2 3 x/wk) or to UVR + sodium arsenite (5 mg/L in drinking-water) and fed laboratory chow supplemented or not with Vitamin E (α-tocopheryl acetate, 62.5 IU/kg diet) or organoselenium (1,4-phenylene*bis*(methylene) selenocyanate (*p*-XSC), 10 mg/kg diet) for 26 wk.	~95% of the tumours were SCCs. Few papillomas, fibrosarcomas and premalignant hyperplasias were also seen. Average tumour/mouse: UVR–3.60 UVR + Vitamin E–2.53 UVR + p-XSC–3.33 UVR + arsenite–7.0 UVR + arsenite + Vit E–3.27 UVR + arsenite + p-XSC–3.40	The first tumour appeared in mice exposed to UVR + arsenite at 10 wk after beginning UVR exposure, whereas the first tumour in mice exposed to UVR alone appeared after 12 wk of UVR exposure. Mice exposed to UVR plus arsenite exhibited an enhanced tumour yield (1.94-fold) compared with mice exposed to UVR alone. Vitamin E and p-XSC reduce tumour yield in mice given UVR + arsenite (2.1 and 2.0 fold respectively). Vitamin E but not p-XSC reduces tumour yield induced by UVR alone
Mice, SK1-hrBR (F) 182 d Davidson *et al.* (2004)	12-19 animals/group Animals were exposed to: - UVR alone (1.2 kJ/m^2, from 3 FS 20 and 1 F-20T12-BL lamps; 85% UVB, 4% UVA), - K_2CrO_4 alone (2.5 and 5.0 ppm in drinking-water), - or combination of UVR + K_2CrO_4 (0.5, 2.5, and 5.0 ppm). Exposure to UV started 1 mo after the initial chromate exposure, 3 ×/wk (every other d) for the first 3 mo, then 2 x /wk (Monday and Wednesday) for 3 further mo.	No tumour in untreated mice and mice treated with chromium alone. Dose-dependent increase in the number of skin tumours (SCCs > 2 mm) in mice exposed to K_2CrO_4 and UV compared with mice exposed to UV alone: 2.63 and 5.02 tumours/ mouse for 2.5 and 5.0 ppm K_2CrO_4 *vs* 0.8 ($P < 0.05$).	Proportion of malignant tumours per mouse: - UV alone: 0.55. - UVR + 5 ppm K_2CrO_4: 0.73

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, SK1-hrBD (M, F) 6 mo Uddin *et al.* (2007)	10 animals/group Weanling mice were exposed to: - UVR (1.0 kJ/m^2, 3 ×/wk) for 26 wk, - UVR + 2.5 or 5.0 ppm potassium chromate, - UVR + 20, 100 or 500 ppm nickel chloride in drinking-water. Vitamin E or selenomethionine was added to the laboratory chow for 29 wk beginning 3 wk before the start of UVR exposure.	96% of the tumours were SCCs and 4% were papillomas Cancers/mouse: - Male: UVR: 1.9 ± 0.4 UVR + 2.5 ppm K_2CrO_4: 5.9 ± 0.8 UVR + 5 ppm K_2CrO_4: 8.6 ± 0.9 - Female UVR: 1.7 ± 0.4 UVR + 20 ppm $NiCl_2$: 2.8 ± 0.9 UVR + 100 ppm $NiCl_2$: 5.6 ± 0.7 UVR + 500 ppm $NiCl_2$: 4.2 ± 1.0	Chromium and nickel significantly increase the UVR-induced skin cancer yield in mice. Chromate caused a more rapid cancer induction (percentage of mice with cancer) in mice given UVR plus chromate: at 18 wk of UVR exposure, 50% of mice given UVR alone developed at least one cancer compared to 80% of mice given UVR + 2.5 ppm chromate and 100% of mice given UVR + 5.0 ppm chromate. Final cancer incidence: – UVR: 80% - UVR + chromate (2.5 and 5.0 ppm): 100%. Neither vitamin E nor selenomethionine reduced the cancer yield enhancement by chromium.
Mice Skh:HR-1 hairless (F) 232 d Reeve *et al.* (1996)	15 animals/group Animals were: - pre-fed for 4 wk on diets designed to provide 20% by weight of fat, comprising 0.5%, l%, 15% or 20% polyunsaturated sunflower oil (balance: hydrogenated cottonseed oil), - exposed to an incremental SSUV radiation regime for 10 wk, 5 d per wk, cumulative doses 111 J/m^2 UVB and 2 106 kJ/m^2 UVA. Feeding of the prepared diets continued until d 232 from commencement of the UV irradiation, when the experiment was terminated.	First tumours appear - by d 84 in mice fed the highest polyunsaturated fat, - by d 113 in mice fed the lowest polyunsaturated fat. CHS reactions in those groups supporting the highest tumour loads (fed 15% or 20% polyunsaturated fat), were significantly suppressed in comparison with the mice bearing smaller tumour loads (fed 0.5% or 10% polyunsaturated fat).	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Opossum *M. domestica* (M, F) 12–24 mo Sabourin *et al.* (1993), Kusewitt *et al.* (2000)	32-62 animals/group; 31 controls Shaved or unshaved animals exposed to 250–500 J/m^2, 3 x/wk, from a bank of FS40 lamps (280 to 400 nm), rate 4 W/m^2, for ≈1 yr. Immediately after UV irradiation, half of the animals are exposed to visible light (60 or 90 minutes) to remove pyrimidine dimers by photoreactivation. Controls exposed to photoreactivating light. To prevent photoreactivation, animals are maintained under red light.	Corneal tumours develop in nearly 100% animals. 154 tumours examined histologically: - 134 fibrosarcomas, - 18 haemangiosarcomas - 2 squamous cell carcinomas overlaying sarcomas Post-UVR exposure to photoreactivating light delays the onset of eye tumours and reduces overall tumour incidence	The South American opossum *Monodelphis domestica* possesses a photolyase enzyme that catalyses the monomerization of UV-induced pyrimidine dimers in DNA. UVR effects reduced by photoreactivation can be attributed to pyrimidine dimers formation.

BCCs, Basal Cell Carcinomas; CHS, Contact Hypersensitivity; d, day or days; h, hour or hours; min, minute or minutes; mo, month or months; NR, not reported; SCCs, Squamous Cell Carcinomas; SCTs, Spindle Cell Tumours; SSUV, simulated solar UV radiation; TNFα, tumour necrosis factor α; vs, versus; wk, week or weeks; yr, year or years

skin. Using the v-Ha-*ras* transgenic Tg.AC mouse line, sensitive to tumour promoters, Trempus *et al.* (1998) have shown that SCCs and SCTs developed within 18-30 weeks following the initial UVR exposure and that in contrast to other mouse stains used in photocarcinogenesis studies, few *Tp53* mutations were found in Tg.AC UV-induced skin tumours, although all Tg.AC tumours express the v-Ha-*ras* transgene. Other strains of transgenic mice, FVN/B strains 215 and 224, which overexpress protein kinase C epsilon (PKCε) and are highly susceptible to the induction of skin tumours by chemical carcinogens, also show increased susceptibility to the induction of skin tumours by UVR. *PKCε* transgenic mice were observed to be highly sensitive to the development of papilloma-independent metastatic squamous cell carcinomas elicited by repeated exposure to UVR (Wheeler *et al.*, 2004, 2005). In studies using Skh-1 mice, exposure to UVR induced a statistically significant increase in the number of malignant skin tumours per mouse, mainly SCCs when compared to controls (Rossman *et al.*, 2002; Burns *et al.*, 2004; Davidson *et al.*, 2004; Uddin *et al.*, 2005, 2007). Dietary polyunsaturated fat enhances the development of UVR-induced tumours in Skh-1 mice, this enhancement being mediated by a modulation of the immunosuppression caused by chronic UV irradiation (Reeve *et al.*, 1996).

3.1.2 Opossum (*Monodelphis domestica*)

Unlike laboratory rodents, a small marsupial, the South American opossum *Monodelphis domestica* possesses the ability to remove cyclobutane-pyrimidine dimers by photoreactivation, a light-dependent process of enzymatic monomerization. *M. domestica* is sensitive to UVR, and, when photoreactivation is prevented, develops primary tumours of the skin and eye in response to chronic exposure to low doses of UVR. Virtually all *M. domestica* chronically exposed to low doses of UVR develop primary corneal tumours; post-UVR exposure to photoreactivating light delays the onset of eye tumours and reduces overall tumour incidence (Sabourin *et al.*, 1993, Kusewitt *et al.*, 2000).

3.2 Melanoma

3.2.1 Transgenic mice exposed to ultraviolet radiation

See Table 3.2

In the mouse, wild-type animals are resistant to malignant melanoma (MM) development even when exposed to repeated treatments with ultraviolet radiation. Chronic UVR treatment regimens, however, have increased MM penetrance by up to 26% in mice carrying various transgenes capable of inducing spontaneous MM development, or melanocytic hyperplasia.

Inbred lines of transgenic Tyr-SV40E mice, having an integrated recombinant gene comprised of the tyrosinase promoter, expressed in pigment cells, and the simian virus 40 early-region transforming sequences spontaneously develop ocular and cutaneous melanomas (Bradl *et al.*, 1991). UVB irradiation of 2–4-day old Tyr-SV40E transgenic mice of either moderate or low susceptibility lines induce skin melanoma (Klein-Szanto *et al.*, 1994; Kelsall & Mintz, 1998).

The pigment-producing cells in TP*ras* transgenic mice express a mutated human T-24 Ha-*ras* driven by a 2.5 kb promoter region from the mouse tyrosinase gene. The *ras* transgenic mice exhibit an altered phenotype, including melanocytic hyperplasia and a muted agouti coat, indicative of hyperproliferative melanocytes. Topical 7,12-dimethylbenz[*a*]anthracene (DMBA) treatment of TP*ras* mice resulted in a high incidence of melanomas. UV light exposures induced papillomas in TP*ras*-negative littermate and melanomas in some albino TP*ras* mice (Broome Powell *et al.*, 1999). When Hacker *et al.* (2005) treated brown mice (mixed C3H/Sv129 strain background) carrying a melanocyte-specific

Table 3.2 Melanomas induced in transgenic mice exposed to ultraviolet radiation

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, C57Bl/6 Tyr-SV40E, moderately susceptible line 9 (M, F) Duration (NR) Klein-Szanto *et al.* (1994)	19, 11 controls Exposed to 328 mJ/cm^2 UVB (20 min/d) for up to 4 consecutive d.	Melanocytic lesions resembling macules, nevi, or early melanomas gradually appeared in the irradiated mice (not in unirradiated transgenic controls of similar age). 20 wk after irradiation, skin samples containing 26 selected lesions were grafted to low susceptibility line 12 mice. - 10/26 selected lesions in 7 of the grafts gave rise to melanomas - all melanomas had ulcerated and two had metastasized.	Eye melanomas develop before any skin melanomas and are fatal in young mice of the more susceptible lines; less susceptible mice have much later onset eye tumours and longer lives. Skin melanomas were obtained in the absence of advanced eye melanomas by grafting skin from high susceptibility (unirradiated) donors to low susceptibility hosts, thereby greatly prolonging the life of the donor skin.
Mice, C57Bl/6 Tyr-SV40E, low susceptibility line 12 (M, F) Duration (NR) Kelsall & Mintz (1998)	112, 71 controls Exposed on each of 3–10 d to 0.22–0.42 J/cm^2 UV radiation from F40 sunlamps (65% UVB), totaling 1.1–3.7 J/cm^2 (8 protocols) Controls: non transgenic C57BL/6 mice.	14 melanomas in 80 (18%) mice surviving at 4 wk, latency: 37–115 wk, metastases in 5/14 (35%) mice The most favourable protocol (1.9 J/cm^2 total UVR, at 0.38 J/cm^2/d for 5 d starting at 3 d of age) led to the highest incidence of melanoma, 5 of 19 (26%) mice and one of the lowest mortality rates, 2 of 19 (10%).	Among the 80 transgenic survivors, 40% of the mice had from one to four keratoacanthomas on the tail. Most arose 6–8 mo after UVR; one-fifth of the lesions regressed spontaneously in 8–20 mo after detection. Keratoacanthomas also arose on the tails of 4 of the group of 16 surviving C57BL/6 nontransgenic controls treated with UVR.
Mice, TP*ras* (M, F) 45 wk Broome Powell *et al.* (1999)	10 animals/group, 18 controls (TP*ras*-negative littermates) - Irradiated 2 x/wk for 38 wk from FS40T12 UVB lamps (> 90% UVB), - Initial dose 5.6 kJ/m^2, increased twice by 20%, up to a total final dose of 8.06 kJ/m^2.	Melanocytic naevi and melanomas develop in 20% irradiated mice.	The TP*ras* mice that developed melanoma had an albino coat colour
Mice C3H/Sv129, TP*ras* (M, F) Duration (NR) Hacker *et al.* (2005)	10-18, 42 controls Exposed to a single total dose of 8.15 kJ/m^2 from FS40 lamps (UVA 320–400 nm, 2.36 kJ/m^2 UVB 280–320 nm, 5.77 kJ/m^2, UVC 250–280 nm, 0.02 kJ/m^2)	UVR irradiated mice (n = 14) developed in situ cutaneous MM with a penetrance of 57% by 12 mo, none of the untreated controls (n = 42) developed tumours	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice C3H/Sv129 Cdk4/TP*ras* (M, F) Duration (NR) Hacker *et al.* (2006)	2–3 d old *Cdk4*$^{R24C/R24C}$, *Cdk4*$^{R24C/R24C}$/TP*ras*, *Cdk4* $^{R24C/+}$/TP*ras* mice Exposed to a single total dose of 8.15 kJ/m^2 from FS40 lamps	*Cdk4*$^{R24C/R24C}$ mice did not develop melanoma, spontaneously or after neonatal UVR. TP*ras* mice developed neonatal UVR-induced, but not spontaneous, melanomas. 58% of mice homozygous for the *Cdk4-R24C* mutation and also carrying the melanocyte-specific activated H*ras* (*Cdk4*$^{R24C/R24C}$/TP*ras*) developed melanoma spontaneously. UVR treatments increased the penetrance of tumour development to 83% (and from 0% to 40% in *Cdk4*$^{R24C/+}$/TP*ras* mice) and decreased the age of onset compared with untreated animals.	Lesions were mainly dermal melanomas, often multicentric, usually accompanied by epidermal hyperplasia in UVR treated animals. The increased melanoma susceptibility in mice carrying both activated Cdk4 and H*ras* is underlined by their increased propensity to develop multiple primary melanomas. All melanoma-bearing UVR-treated *Cdk4*$^{R24C/R24C}$/TP*ras* animals developed more than one primary lesion, significantly more than untreated *Cdk4*$^{R24C/R24C}$/TP*ras* mice (40%, $P = 0.012$) or UVR-treated TP*ras* mice (16%, $P = 0.001$).
Mice, albino FVB, HGF/SF (M, F) 13 mo Noonan *et al.* (2001)	Number/group at start (NR) UV-irradiated at: – group A, 3.5 d and again at 6 wk; – group B, 6 wk; – group C, 3.5 d; – group D, no UV treatment. Neonatal mice received a single treatment of 9.58 kJ/m^2 from Phillips F40 UV lamps (UV-A, 320–400 nm, 3.31 kJ/m^2; UV-B, 280–320 nm, 6.24 kJ/m^2; UV-C, 250–280 nm, 0.03 kJ/m^2). 6-wk-old mice received a single treatment of 19.16 kJ/m^2.	Only mice from groups A and C developed melanoma. No melanoma in non-transgenic or untreated transgenic mice (observation: 13 mo). Melanoma development in HGF/SF transgenic mice after UV irradiation at both 3.5 d and 6 wk (group A) identical to that seen after only a single exposure at 3.5 d (group C). UV irradiation (group B) was not tumorigenic.	The second UV exposure increased the multiplicity of melanocytic lesions as well as the incidence of non-melanocytic tumours.

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, albino FVB, HGF/SF (M, F) 14 mo De Fabo *et al.* (2004)	Number/group at start (NR) Neonatal HGF/SF-transgenic mice irradiated at 3–5 d of age with a source coupling UV interference or cutoff filters to a 2.5 kW xenon arc lamp, to produce UVB or UVA wavebands or solar simulating radiation (UVB + UVA + visible radiation in proportions approximating sunlight). Neonatal transgenic animals also irradiated with F40 sunlamps, (UVB + UVA radiation and visible light). Total UVvis doses (kJ/m^2): Xenon UVB filter: 14.0 unfiltered F40 lamp: 14.7 solar simulator: 322.1 mylar filtered F40: 14.1 Xenon UVA filter: 150 (UVB and solar simulator doses are equivalent to 23 standard erythemal doses) UVB dose 14.0 kJ/m^2 UVA dose 150 kJ/m^2	Incidence of MM Xenon UVB filter: 10/18 unfiltered F40 lamp: 6/23 solar simulator: 5/29 mylar filtered F40: 1/20 Xenon UVA filter: 0/23	UVB highly effective at initiating melanoma. A further group of animals was irradiated with 4.5 kJ/m^2 of UVB (7 SED), which was also effective at initiating melanoma (not shown). UVA radiation did not initiate any melanomas. Removal of UVB from the broadband F40 source prevented the initiation of melanoma. Median time to first melanoma (d): Xenon UVB filter: 127 unfiltered F40 lamp: 169 solar simulator: 284
Mice XPA (–/–), SCF-Tg 24 mo Yamazaki *et al.* (2005)	Number/group at start (NR) Irradiated 3 x/wk for 10 wk, 5 J/cm^2 UVB (total dose: 150 J/cm^2), from FL.20SE.30; fluorescent lamps (55% radiation within the UVB range (305 nm), 25% and less than 1%, within UVA and UVC, respectively).	55% of UV-treated XPA (–/–), SCF-Tg mice develop melanoma at 70 wk after UVB radiation. Lentigo maligna melanoma appear 4 mo after the termination of UVR exposure. At 6 mo, some mice developed nodular melanoma. No melanoma develop in UV-treated XPA-normal, SCF-Tg mice and non-treated XPA -(–/–), SCF-Tg mice.	

d, day or days; F, female; h, hour or hours; M, male; min, minute or minutes; MM, malignant melanoma; mo, month or months; NR, not reported; SED, standard erythemal dose; wk, week or weeks; yr, year or years

mutant *Hras* (G12V) transgene (TP*ras*), with a single neonatal UVR dose of (8.15 kJ m^2), 57% of the UV irradiated mice developed in situ cutaneous MM by 12 months, whereas none of the untreated controls developed tumours. In another study by the same author, UVR treatment greatly increased the penetrance and decreased the age of onset of melanoma development in *Cdk4*$^{R24C/R24C}$/TP*ras* animals compared with TP*ras* alone (Hacker *et al.*, 2006).

However, murine melanocytic tumours are dermal in origin and lack the epidermal component that characterizes human melanoma. However, the skin of transgenic mice in which a metallothionein-gene promoter forces the overexpression of hepatocyte growth factor/scatter factor (HGF/SF) has melanocytes in the dermis, epidermis and dermal–epidermal junction, and is thus more akin to human skin. Untreated HGF/SF-transgenic mice are already genetically predisposed to late-onset melanoma. Using these transgenic mice, Noonan *et al.* (2001) showed that a single UV irradiation of neonates is sufficient to induce early onset melanoma in the majority of animals, while UV irradiation of 6-week-old mice is insufficient. Using the same model, it was further shown that UVB and not UVA is effective at initiating melanoma (De Fabo *et al.*, 2004).

Xeroderma pigmentosum group A gene-deficient (XPA–/–), stem cell factor-transgenic (SCF-Tg) mice are defective in the repair of damaged DNA and do have epidermal melanocytes. Following chronic UVB irradiation, these mice develop lentigo maligna and nodular melanomas (Yamazaki *et al.*, 2005).

3.2.2 Human melanocytes grafted to immunodeficient mice exposed to ultraviolet radiation

See Table 3.3

Atilasoy *et al.*, have developed an experimental model in which full-thickness human skin is grafted to immunodeficient recombinase activating gene-1 (RAG-1) knockout mice (Atillasoy *et al.*, 1998). Chronic UVB irradiation with or without an initiating carcinogen can induce human melanocytic lesions, including melanoma. It was further shown that overexpression of basic fibroblast growth factor (bFGF) via adenoviral gene transfer in human skin xenografted to severe combined immunodeficiency mice led to black pigmented macules within 3 weeks of treatment, and to melanoma when bFGF was combined with UVB (Berking *et al.*, 2001).

In contrast with experiments using neonatal foreskin, no melanocytic lesions were induced when adult skin was used (Berking *et al.*, 2002). In normal human skin grafted onto severe combined immunodeficient mice (SCID), an increased expression of a combination of three growth factors, bFGF, stem cell factor, and endothelin-3, along with exposure to UVB can transform normal melanocytes into a melanoma phenotype within 4 weeks. Invasion of melanoma lesions was found in skin from newborn donors, whereas melanomas in adult skin were of a non-invasive in situ type only. This suggests that susceptibility of skin to exogenous tumour promoters is dependent on age (Berking *et al.*, 2004).

3.2.3 Opossums

See Table 3.4

Chronic UVB irradiation of suckling young opossums (*M. domestica*) induces nevi and melanoma that progress to metastasis (Robinson *et al.*, 1994, 1998) suggesting that in this species, UVB can act as a complete carcinogen, inducing precursor lesions and driving progression to metastatic melanoma.

3.2.4 Fish

See Table 3.5

Interspecies hybrids and backcrosses of platyfish (*Xiphophorus maculatus*) and swordtails

Table 3.3 Melanomas induced in human melanocytes grafted to immunodeficient mice exposed to ultraviolet radiation

Species, strain (sex) Duration Reference	Animals/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Mice, RAG-1 (M, F) Duration (NR) Atillasoy *et al.* (1998)	Number/group at start (NR) 8–12 wk old mice grafted with full-thickness human foreskin. 4 groups: after 4-6 wk: no treatment, a single treatment with 7,12- dimethyl(a) benzanthracene (DMBA), UVB irradiation at 500 J/m^2 alone 3 ×/wk, and a combination of DMBA and UVB.	9/40 (23%) of human foreskin grafts treated with UVB only, and 18/48 (38%) of grafts treated with the combination of DMBA + UVB developed solar lentigines within 5 to 10 mo. 73% of of all UVB-treated xenografts develop melanocytic hyperplasia 1 melanoma (nodular type) out of 48 DMBA+UVB treated xenografted mice.	
Mice, SCID (M, F) Duration (NR) Berking *et al.* (2001)	Number/group at start (NR) Human skin xenograft injected intradermally with adenoviral vector bFGF/Ad5, exposed 3 ×/wk for 10 min to 30–50 mJ/cm^2 UVB from FS72/T12 UVB lamps throughout a period of 2 to 10 mo.	1 lentiginous melanoma in an adult abdominal skin graft after 2 mo (7 bFGF/Ad5 injections and 26 UVB irradiations).	
Mice, SCID and RAG-1 (M, F) Up to 22 mo Berking *et al.* (2002)	155 adult human skin specimens grafted onto SCID or RAG-1 mice, irradiated 2–3 ×/wk with 40 mJ/cm^2 UVB over a period of up to 10 mo with or without beforepical application of DMBA.	Only actinic keratoses and 1 squamous cell carcinoma. No melanocytic lesions.	Melanocytes from young individuals may be more susceptible to the transforming effect of genotoxic agents than melanocytes from adults.
Mice, SCID (M, F) Duration (NR) Berking *et al.* (2004)	Human skin xenografts (neonatal foreskin or adult skin) injected intradermally with adenoviral vectors bFGF/Ad5, ET-3/Ad5, SCF/Ad5 exposed 3 ×/wk to 30 – 50 mJ/cm^2 UVB from FS72/T12 UVB lamps throughout a period of 4 wk.	17/50 invasive melanomas in newborn foreskin. in situ melanomas in 45–56% of adult skin grafts exposed to the three growth factors independent from the exposure to UVB.	Lesions regressed upon withdrawal of the growth factor stimulation after 4 wk.

bFGF, basic fibroblast growth factor; d, day or days; ET-3, endothelin-3; F, female; M, male; mo, month or months; NR, not reported; SCF, steam cell factor; wk, week or weeks

Table 3.4 Melanomas induced in South American opossum *M. domestica* exposed to ultraviolet radiation

Species, strain Reference	Number/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
South American opossum (*M. domestica*) Duration (NR) Robinson *et al.* (1994)	- 43 litters of suckling young were irradiated with sunlamps with a spectral emission peak at 302 nm (UVB) to induce melanocytic nevi. Total doses of 0.87–5.0 kJ/m^2 were divided equally among up to 14 exposures during the 19 d from birth. – 13 litters received doses of 125 J/ m^2 of UVB every other d, for up to 19 d after birth, with a maximum total dose of 1.12 kJ/rn^2. - 30 litters received different total doses, up to a total dose of 5.0 kJ/ m^2. Affected animals were then exposed 3 times/wk to 125 J/ m^2 of UVB for up to 45 wk to promote progression to malignancy.	Of 358 sucklings exposed, 217 (60%) survived to weaning, and 22 (6%) possessed a nevus at weaning. Nevi of 8 of the 20 chronically-exposed animals progressed to malignant melanoma with metastases to lymph node(s).	
South American opossum (*M. domestica*) Duration (NR) Robinson *et al.* (1998)	620 suckling young were exposed to ultraviolet radiation (UVR, predominantly UVB: 290–320 nm) to determine an optimal protocol for induction and progression of melanoma (7 protocols).	The lowest dose (175 J/ m^2) administered three times a wk for three wk led to the highest incidence of melanotic lesions with melanoma potential (8.1%) among young (5-mo-old) adults. Among 101 much older animals (> 17 mo at necropsy), 43% showed metastatic melanoma to the lymph nodes and almost one-third of these had progressed to widespread dissemination.	In the opossum, UVR can act as a complete carcinogen for progression to widely disseminated disease and exposure of sucklings can lead, in old age, to widespread metastatic melanoma in this model.

d, day or days; NR, not reported; wk; week or weeks

Table 3.5 Melanomas induced in Platyfish-swordtail hybrids exposed to ultraviolet radiation

Species, strain (sex) Duration Reference	Number/group at start Exposure regimen: radiation type, dose, dose rate	Results Target organ Incidence and/or multiplicity of tumours (%)	Comments
Platyfish (X. *maculatus*)-swordtail (*X. Helleri*) hybrids (M, F) up to 6 mo Setlow *et al.* (1989)	A total of 5000 fish. Multiple exposures on 5-20 consecutive days beginning on d 5 after birth (150 to 1700 J/ m^2/d) or a single exposure of = 200 J/ m^2/d of $\lambda > 304$ nm from FS-40 sunlamps, filtered by a thin acetate film ($\lambda > 290$ nm), or a thin Mylar film ($\lambda > 304$ nm), or a thick plastic sheet ($\lambda > 360$ nm).	Tumor prevalence: 20% to 40% at 4 mo of age, (background rates: 12% in strain 1, and 2% in strain 2).	Exposure of the fish to visible light after UV exposure reduces the prevalence to background.
Platyfish (X. *maculates*)-swordtail (*X. Helleri*) hybrids (M, F) 4 mo Setlow *et al.* (1993)	Groups of five 6-d-old fish submitted to a single irradiation - from a filtered ($\lambda > 304$ nm) sunlamp - or with narrow wavelength bands at 302, 313, 365, 405, and 436 nm and scored for melanomas 4 mo later.	Single exposures to filtered sunlamp radiation: - up to 42% melanomas for (850 J/m^2). The action spectrum (sensitivity per incident photon as a function of wavelength) for melanoma induction shows appreciable sensitivity at 365, 405, and probably 436 nm.	Only heavily pigmented animals are susceptible to melanoma induction by a single, relatively small exposure to UV.

d, day or days; F, female; M, male; mo, month or months

(*Xiphophorus helleri*) eventually develop genetically determined spontaneous melanoma (the Gordon-Kosswig melanoma). Setlow *et al.* (1989) have developed two strains of these fishes that are susceptible to invasive melanoma induction by exposure to filtered radiation from sunlamps in the wavelength ranges $\lambda > 290$ nm and $\lambda > 304$ nm. Irradiation of these fishes and of *X. maculatus*/*X. couchianus* hybrids with narrow wavelength bands show that the action spectrum for melanoma induction shows appreciable sensitivity at 365, 405, and probably 436 nm, suggesting that wavelengths not absorbed directly in DNA are effective in induction (Setlow *et al.*, 1993).

3.3 Synthesis

Recent studies have mainly focused on the mechanisms of UV-induced carcinogenesis and have used specific strains of mice (sencar mice). Several studies conducted examining the tumorigenic effects of solar radiation, broad-spectrum ultraviolet radiation, UVA, UVB and UVC in experimental animals, since 1992, support and confirm the conclusions of the previous *IARC Monograph*.

Solar radiation causes squamous-cell carcinoma of the skin and of the conjunctiva in mice and rats.

Broad-spectrum UVR causes squamous-cell carcinoma of the skin and of the cornea/conjunctiva in mice and rats.

UVA causes squamous-cell carcinoma of the skin in mice.

UVB causes squamous-cell carcinoma of the skin in mice and opossum and invasive skin melanomas in platyfish-swordtail hybrid fish and opossum.

UVB causes skin melanomas in transgenic mice and skin melanomas in genetically engineered immunocompromised mice grafted with human melanocytes.

UVC causes squamous-cell carcinoma of the skin in mice.

4. Other Relevant Data

4.1 Transmission and absorption in biological tissues

UVR may be transmitted, reflected, scattered or absorbed by chromophores in any layer of tissue, such as the skin and the eye. Absorption is strongly related to wavelength, as it depends on the properties of the responsible chromophore(s) (IARC, 1992).

UVC (200–280 nm) has the highest energy and thus is potentially the most damaging to biological tissues. However, because of its absorption by the ozone layer, its impact on human health is largely theoretical except for occasional artificial UV sources. UVB (280–315 nm) makes up only 5–10% of the UVR that penetrates the ozone layer but because of its ability to directly damage DNA-forming modified bases, understanding molecular and cellular links between UVB exposure and carcinogenesis has continued to be a major focus since the previous *IARC Monograph* (IARC, 1992). The role of non-DNA chromophores in UV carcinogenesis has been extensively studied over the past 15 years in particular in relation to UVA (315–400 nm) exposure. UVA, in addition to inducing a variety of DNA damage, also penetrates the dermis where it interacts with proteins and lipids resulting in skin ageing (for a review, see Ridley *et al.*, 2009).

4.1.1 Eye

The eye is a complex multilayered organ. The retina at the back of the eye receives visible radiation and the intermediate layers attenuate UVR to different degrees, thereby protecting the retina from photodamage. The outermost cornea absorbs UVC (from artificial sources) and a substantial amount of UVB, which is further attenuated by the lens and the vitreous humour in front of the retina. UVA is less attenuated by the cornea than by the internal structures, and

does not reach the retina (for a review, see Young, 2006). Age-related changes in lens crystallins affect their structure and function causing the lens to increasingly scatter light on the retina, and causing the lens to become opaque (for a review, see Sharma & Santhoshkumar, 2009)

4.1.2 Skin

The skin comprises two main layers (for a review, see Young, 2006):

1) the outer acellular and cellular epidermis, and
2) the inner largely extracellular dermis.

Keratinocytes are the main epidermal cell type, which differentiate to create the outermost, non-living, terminally differentiated, cornified and protective stratum corneum. The dividing cell population is located in the innermost basal layer of the epidermis. Dendritic pigment-producing melanocytes and immunocompetent dendritic Langerhans cells are also present in the epidermis. The dermal connective tissue is mostly collagen synthesized by fibroblasts. The dermis contains the skin's vascular supply. Significant differences have been found in the UVA and UVB absorption properties of different skin types (Antoniou *et al.*, 2009).

4.2 Genetic and related effects: consequences of UVR exposure

4.2.1 Photoproduct formation

(a) DNA photoproducts: direct and indirect formation

A multitude of photoproducts, the ratio of which depends markedly on wavelength, are formed in cellular DNA by solar UVR (IARC, 1992). The question of which types of DNA damage are formed by UVA, UVB and UVC has been extensively studied. Unlike UVB, UVA is weakly absorbed by DNA and the primary method of DNA-damage induction by UVA occurs indirectly via photosensitizers, which include endogenous melanins or proteins containing porphyrin, haem or flavin groups. They can also be exogenous, e.g. antibacterial agents such as naladixic acid and fluoroquinolones or the immunosuppresive drug azathioprine (for a review, see Ridley *et al.*, 2009), and 8-methoxypsoralen (methoxsalen) in combination with UVA (PUVA) used for photochemotherapy. These exogenous chemicals absorb in the UVA range and release reactive oxygen species (IARC, 2012), and thus mediate UVA-induced DNA damage. The excited sensitizers may react with DNA directly by one-electron transfer (Type I mechanism) and/or via the generation of singlet oxygen ($^1O_2$) by energy transfer to molecular oxygen (major Type II mechanism), giving rise to guanine modifications including 8-oxoguanine. The excited sensitizer can also transfer an electron to oxygen resulting in the formation of superoxide anion radical (O_2^-) (minor Type II mechanism). Disproportionation of O_2^- can give rise to hydrogen peroxide (H_2O_2), and reactive species formed through the interaction of H_2O_2 with metal ions may induce DNA damage (for reviews, see Ridley *et al.*, 2009 and Hiraku *et al.*, 2007).

In addition to the generation of reactive oxygen species, reactive nitrogen species such as nitric acid and peroxynitrite are formed after UVA exposure. UVA irradiation can also lead to the long-term cellular generation of both reactive nitrogen species and reactive oxygen species (Didier *et al.*, 1999; Valencia *et al.*, 2006), indicating the possibility of a prolonged effect of a single UVA exposure (see Section 4.2.3).

Several studies *in vitro* have shown a predominance of oxidized purines after UVA-induced oxidative damage with relatively few strand breaks or oxidized pyrimidines (Kielbassa *et al.*, 1997; Pouget *et al.*, 2000). However, thymidine-derived cyclobutane–pyrimidine dimer lesions have been detected after UVA exposure in several cell models (e.g. Chinese hamster ovary cells) (Douki

et al., 2003), and in human skin (Courdavault *et al.*, 2004; Mouret *et al.*, 2006), recently reviewed by Ridley *et al.* (2009). Moreover, in human skin after exposure to UVA, cyclobutane–pyrimidine dimer lesions rather than oxidative lesions were the main type of DNA damage induced (Mouret *et al.*, 2006). It has been suggested that UVA may generate cyclobutane–pyrimidine dimer lesions via a photosensitized triplet energy transfer in contrast to formation via direct excitation of DNA by UVB (Douki *et al.*, 2003; Rochette *et al.*, 2003).

(b) Other chromophores

In addition to DNA, many other cellular components absorb and/or are damaged by solar UVR (IARC, 1992). Non-DNA chromophores and targets are particularly relevant at longer wavelengths. For instance *trans*-urocanic acid, a deamination product of histidine, is an important chromophore found in high concentrations in the stratum corneum. *Trans*-urocanic acid undergoes a photoisomerization to *cis*-urocanic acid in the presence of UVR, which has immunoregulatory properties (Norval, 2006).

4.2.2 Mutagenicity

Numerous reports show that sunlight or solar-simulated radiation induces mutations in bacteria, plants, mammalian cells, Chinese hamster ovary and lung (V79) cells, mouse lymphoma cells, and human skin fibroblasts. Studies in bacteria exposed to radiation throughout the solar UV spectrum demonstrate mutagenic activity unambiguously. UVA (320–400 nm) is mutagenic to yeast and cultured mammalian cells; UVB (290–320 nm) to bacteria and cultured mammalian cells; and, UVC (200–290 nm) to bacteria, fungi, plants, cultured mammalian cells, including Chinese hamster ovary and V79 cells, and human lymphoblasts, lymphocytes and fibroblasts. Because wavelengths in the UVC range do not reach the surface of the Earth, they are of no significance as a source of damage in natural sunlight (IARC, 1992).

DeMarini *et al.* (1995) evaluated the mutagenicity and mutation spectra of a commercial tanning salon bed, white fluorescent light and natural sunlight in four DNA-repair backgrounds of *Salmonella*. Approximately 80% of the radiation emitted by the tanning bed was within the UV range (250–400 nm), whereas only ~10% of the sunlight and 1% of the fluorescent light were in the UV range. The tanning bed emitted similar amounts of UVA (315–400 nm) and UVB (280–315 nm), whereas sunlight and fluorescent light emitted, respectively, 50–60 times and 5–10 times more UVA relative to UVB. Based on total dose (UV + visible, 400–800 nm), the mutagenic potencies (revertants × 10^{-3}/J/m^2) of the exposures in strain TA100 were 3.5 for sunlight, 24.9 for fluorescent light, and 100.6 for the tanning bed. Thus, the tanning bed was 29 times more mutagenic than sunlight. The mutagenic potency of the tanning bed was similar to that produced by pure 254-nm UV (DeMarini *et al.*, 1995).

DNA-sequence analysis of the revertants of strain TA100, which is a base-substitution strain, was performed at the doses that produced 10-fold increases in the mutant yields (revertants/plate) compared to the control plates for sunlight and fluorescent light, and a 16-fold increase for the tanning bed. Thus, more than 90% of the mutants analysed were induced by the exposures as opposed to being spontaneous in origin. More than 80% of mutations induced by all three exposures were G:C→A:T transitions, and 3–5% were presumptive or identified multiple mutations. The frequencies of the multiple mutations were increased 38–82-fold in TA100 by the exposures, with 83% (19/23) of these multiple mutations induced by the tanning bed being CC→TT tandem mutations. Thus, DeMarini *et al.* (1995) also showed that a tanning bed produced a mutation spectrum similar to that found in the *TP53* gene in sunlight-associated skin tumours (Dumaz *et al.*, 1994).

4.2.3 Mutation profiles and target genes

The study of the mutation profiles in skin tumours and in particular those from individuals with either a defect in the repair processes that remove UV-induced DNA damage (e.g. xeroderma pigmentosum (XP) patients or other rare syndromes associated with increased skin cancer risk) has allowed the assessment of the relative contribution of bipyrimidine photoproducts and oxidative damage to the mutagenic effects of UVR, and has provided invaluable models to delineate the genes affecting crucial pathways involved in skin carcinogenesis.

Point mutations found in the *TP53* gene in skin tumours from normal individuals and repair-deficient XP patients are mainly G:C→A:T transitions in skin tumours (74% in non-XP, 87% in XP), and also to a lesser extent in internal tumours (47%) where, however, they are mainly located at 5′CG-3′ dinucleotide (CpG; 63%) sequences—probably due to the deamination of the unstable 5-methylcytosine (Dumaz *et al.*, 1994). In XP skin tumours, 100% of the mutations are targeted at pyrimidine–pyrimidine (py–py) sequences and 55% of these are tandem CC→TT transitions. In skin tumours from normal individuals, 14% of the *TP53* mutations are double mutations and, as in XP skin tumours, all these are CC→TT transitions. In contrast, internal tumours rarely contain tandem mutations (0.8%) and, of these, only 2/14 were CC→TT transitions. A similar mutation profile of C→T or tandem CC→TT UV signature transitions, occurring at bipyrimidine sequences, has been found in several other genes including *PTEN* (phosphatase and tensin homologue deleted on chromosome 10; Ming & He, 2009; Wang *et al.*, 2009). *Ras*, *Ink4a-Arf* as well as alterations of the different partners of the mitogenic sonic hedgehog signalling pathway (patched, smoothed, and sonic hedgehog) have also been found in XP tumours and sporadic skin cancers. The majority of mutations are at C→T or tandem CC→TT transitions (Daya-Grosjean & Sarasin, 2005).

Based on the reactivity of different wavelengths of UVR with DNA, these G:C→A:T transition mutations induced at dipyrimidine sites were considered for many years as specifically resulting from UVB-induced cyclobutane–pyrimidine dimers or pyrimidine (6–4) pyrimidone photoproducts, and termed the "UV-signature" or "UV-fingerprint mutations" (Wikonkal & Brash, 1999), and A:T→C:G transversions were considered as UVA "fingerprint mutations" (Drobetsky *et al.*, 1995; Robert *et al.*, 1996). However, the wavelength specificity of these mutations has been challenged based on recent findings in rodent cell models, mouse models, and human skin. The UVA-induced mutation profile in exon 2 of adenine phosphoribosyltransferase (*Aprt)* gene in rodent cells showed a high proportion of mutations recovered opposite thymine–thymine–dipyrimidine damage sites supporting the notion that cyclobutane–pyrimidine dimers are a premutagenic lesion in UVA-induced mutagenesis (Rochette *et al.*, 2003). C→T transition mutations in the *lacZ* transgene have been detected in the epidermis and dermis of UVA-treated mice, corresponding to the formation of cyclobutane–pyrimidine dimers (Ikehata *et al.*, 2008), in the *Tp53* gene of UVA- or UVB-induced skin tumours in hairless mice (van Kranen *et al.*, 1997), in the *TP53* gene of benign solar keratoses and malignant skin squamous cell carcinomas, in humans (Agar *et al.*, 2004), and in UVA-irradiated human skin cells under certain experimental conditions (Courdavault *et al.*, 2004; Rünger & Kappes, 2008).

Another characteristic of mutations in epithelial skin cancers is the preference of their occurrence for a CpG sequence, which is the consensus target motif for epigenetic DNA methylation in vertebrates. Mutation hotspots in such a sequence context within the *Tp53* gene have been identified, and it has been suggested that

their presence could be used as a marker of solar UV exposure (Ikehata & Ono, 2007; Rochette *et al.*, 2009). However, the specificity of dinucleotide mutability in skin cancer is complex. Lewis *et al.* (2008) compared the base-substitution signatures obtained in several mutation assay model systems after exposure to UVB, UVC or simulated sunlight and cancer-specific base substitutions collated in the IARC *TP53* database (IARC, 2006b), for exons 5, 7 and 8 of the *TP53* gene. The UVB, UVC and skin cancer profiles for exon 5 and 8 all showed relatively high levels of G:C→A:T mutations primarily at TC and CC sites, and to a lesser extent at CT sites. However the exon 7 profiles did not group with the skin cancer profiles which showed a relatively high level of G:C→A:T mutations at CpG sites.

Based on these findings, the back-extrapolation from a mutation to an exposure to a single wavelength region of the UVR spectrum is not possible.

The study of syndromes associated with increased skin cancer risk has been instrumental in the identification of genes critical for UV carcinogenesis. Germline mutations in *PTEN* resulting in altered *PTEN* function, detected in patients with Cowden disease and Bannayan–Riley–Ruvalcaba syndrome (Bonneau & Longy, 2000), are associated with an increased risk of basal cell carcinoma, squamous cell carcinoma, and melanoma (Nuss *et al.*, 1978; Camisa *et al.*, 1984; Liaw *et al.*, 1997; Trojan *et al.*, 2001; Ming & He, 2009). Mice with *Pten* deletion and mutation are highly susceptible to tumour induction (Suzuki *et al.*, 1998). Conditional knockout of *Pten* in skin leads to neoplasia (Li *et al.*, 2002; Suzuki *et al.*, 2003; Backman *et al.*, 2004). *Pten* deficiency in mice causes increases in cell proliferation, apoptotic resistance, stem-cell renewal/maintenance, centromeric instability, and DNA double-strand breaks (Groszer *et al.*, 2001; Kimura *et al.*, 2003; Wang *et al.*, 2006; He *et al.*, 2007; Shen *et al.*, 2007), which can enhance susceptibility to carcinogens and the occurrence of secondary genetic or epigenetic alterations that can lead to skin cancer development. Patients with Gorlin syndrome (or basal cell nevus syndrome) suffer with multiple basal cell carcinoma. This syndrome is associated with mutations in the *Patched* (*PTCH*) gene, an essential component in Hedgehog signalling (Epstein, 2008). Aberrant activation of sonic hedgehog homologue (SHH) signalling, usually because of mutations either in the *PTCH* or smoothened (*SMOH*) genes (Reifenberger *et al.*, 2005) or because of hyperactivation of this pathway, is often found in sporadic basal cell carcinomas.

Dysfunctional p53 is likely to affect protective responses to DNA damage and oncogenic signalling. Experiments in both humans and mice have shown that clusters of epidermal cells with mutant p53 occur long before squamous cell carcinoma becomes visible (de Gruijl & Rebel, 2008). Although *TP53* mutations cause genetic instability and facilitate the carcinogenic process, they are not enough to cause basal cell carcinoma or squamous cell carcinoma, and the activation of signalling cascades (normally needed for cell proliferation and homeostasis) is often also involved. Based on the molecular, pathological and functional dissection of such signalling cascades, evidence has accumulated linking an activated receptor tyrosine kinase (RTK)/RAS pathway in combination with dysfunctional p53 to the development of squamous cell carcinoma; activated Hedgehog pathway with possibly dysfunctional p53 to the development of basal cell carcinoma; and in cutaneous melanoma, activated RTK/RAS pathway in combination with inactivation of the inhibitor of cycline-dependant kinase 4 & 6 (*INK4a*) locus (de Gruijl *et al.*, 2001). The Notch signalling pathway has also been identified as a key regulator of epidermal homeostasis and implicated in skin carcinogenesis; aberrrant Notch signalling leads to skin cancer including basal cell carcinoma, squamous cell carcinoma, and melanoma (Okuyama *et al.*, 2008).

4.2.4 Genomic instability, bystander effect, telomere shortening

Another potential mechanism for inducing genomic instability in cells not directly hit by radiation is via the bystander effect. Bystander effects via both gap-junction and extracellular signalling have been observed in cells following UVB treatment (Banerjee *et al.*, 2005, Dahle *et al.*, 2005), and an UVA-induced bystander effect has been reported that can be attenuated by the use of a nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitor, suggesting a possible role of reactive oxygen species in the induction of this effect (McMillan *et al.*, 2008; Whiteside & McMillan, 2009). After UVA exposure, such mechanisms have been extensively investigated partly because of the action spectra of UVA's interaction with DNA. There is an increasing body of evidence that suggests that UVA-induced (and to some extent UVB-induced) damage cannot only remain but also be generated for prolonged periods in the irradiated cell, its progeny, and also in surrounding cells and tissues which were not themselves exposed. The progeny of cells which have survived irradiation show changes in chromosomal structure and copy number, the generation of micronuclei, changes in gene expression and cell survival (Little, 2000; Morgan, 2003), and are all seen as end-points of genomic instability. Such persistent genomic instability defined as the persistent induction of DNA and cellular damage in irradiated cells and their progeny (Ridley *et al.*, 2009) can lead to a hypermutator phenotype where genetic alterations increase generation upon generation in a large proportion of the progeny of the irradiated cells, increasing the risk of malignant transformation. Conversely, another characteristic of persistent genomic instability can be increased cell-kill of the progeny, meaning that the risk of cancer arising from these cells is reduced rather than increased (Ridley *et al.*, 2009).

For instance, instability was observed for several generations in the GM10115 human–hamster hybrid cell line after combined treatment of UVA with bromodeoxyuridine and Hoechst 33258 dye (Limoli *et al.*, 1998). Both UVA and UVB are able to induce delayed mutations in the hypoxanthine-guanine phosphoribosyltransferase (*Hprt*) gene of V79 Chinese hamster fibroblast cells (Dahle & Kvam, 2003), which could be inhibited by reactive oxygen species scavengers (Dahle *et al.*, 2005). Mutations in the *HPRT* gene have shown to be increased 7 days after UVA irradiation in human keratinocytes HaCaT (Phillipson *et al.*, 2002). In the same cell model, UVA treatment led to continued reductions in survival of UVA-treated HaCaT for over 21 days following treatment, and an increase in the number of micronuclei per cell over the same period. The addition of catalase was shown to reverse these effects to near-control levels. A bystander effect was induced in human keratinocytes HaCaT and fibroblasts MRC5 cells treated with UVA radiation but not UVB radiation (Whiteside & McMillan, 2009). One potential mechanism for the generation of reactive oxygen species under such experimental conditions involves the UVA-induction of enzyme activity. One potential target is a NADPH oxidase (Valencia & Kochevar, 2008). This enzyme has been shown to cause increased superoxide generation in response to UVA in mouse, monkey, and human cell lines (Hockberger *et al.*, 1999). The resulting increase in superoxide and its conversion to other reactive oxygen species would lead to increased cellular and DNA damage. Prolonged generation of reactive oxygen species by such mechanisms in the initially exposed cells and their progeny therefore have the potential to enable persistent genomic instability (Ridley *et al.*, 2009).

Another mechanism for inducing persistent genomic instability is via the shortening and loss of telomeres. The shortening of telomeres or the dysfunction of proteins associated with

the telomeres can lead to large scale transfers of sequences between chromosomes, which lead to the amplification or deletion of sequences (Bailey & Murnane, 2006). It has been demonstrated that UVA can increase the rate of telomere shortening (Oikawa *et al.*, 2001; Ridley *et al.*, 2009), therefore suggesting a possible link between UVA irradiation and increasing instability over several generations.

It has also been shown that irradiation with UVA and UVB is able to trigger increased microsatellite instability in radial growth phase melanoma cells (Hussein *et al.*, 2005).

4.2.5 Cell killing – apoptosis and senescence

Apoptosis and premature senescence are protective mechanisms against the presence of unrepaired DNA lesions in the genome that could otherwise induce mutations increasing the risk of carcinogenesis induced after UV irradiation. The fact that nucleotide excision repair (NER)-deficient cells are very sensitive to the cell-killing effect of UV light is a clear indication that unrepaired photoproducts constitute the main apoptosis-triggering signal after UV irradiation (Batista *et al.*, 2009). How these lesions are processed to generate a toxic signal is unclear. While some data suggest transcription blockage is the main reason behind this apoptosis induction, other data suggest that the formation of DNA double-strand breaks during the replication of cyclobutane-pyrimidine dimers-containing DNA is necessary for the commitment to cell death (Batista *et al.*, 2009). UV light (mainly UVA and UVB) is also able to directly activate membrane death receptors that trigger apoptosis independently of DNA damage. Mitogen-activated protein kinases (MAPKs) are also directly activated by UV light and whether this activation is DNA-damage dependent or independent is still unclear.

The hallmark of cellular senescence is the loss of proliferative capacity, with the accumulation of senescent cells in skin leading to skin aging. Once cells have entered into senescence, they undergo a series of morphological and metabolic changes, and gene-expression profiles are altered as has been shown in human skin fibroblasts after exposure to UVB (Chen *et al.*, 2008).

4.3 Genetic susceptibility: host factors modulating the response to UV

4.3.1 DNA repair capacity and single nucleotide polymorphisms (SNPs) in DNA repair genes

Many of the directly formed UV photoproducts are repaired via the nucleotide excision repair (NER) pathway, and those formed indirectly via the modification of DNA by reactive oxygen species and reactive nitrogen species require components of the base-excision repair pathway.

NER operates through two subpathways in the early stages of damage recognition, depending on whether the damage is located anywhere throughout the genome [global genome (GG) repair] or in an actively transcribed gene [transcription-coupled (TC) repair]. GG repair begins with recognition of the damage by the XPC-RAD23B-centrin2 complex, aided in some cases by the UV damaged DNA-binding activity (UV-DDB) that includes the subunits DDB1 and DDB2/XPE. The mechanisms for TC repair are not completely understood; a current model postulates that the pathway is initiated by the arrest of RNA polymerase II at a lesion on the transcribed strand of an active gene, in a process that requires several factors including the Cockayne syndrome A (CSA), CSB, and XPA-binding protein-2 (XAB2) proteins (Sarasin & Stary, 2007; Hanawalt & Spivak, 2008). The recognition events in GG-NER and TC-NER are followed by a common pathway involving the

unwinding of the damaged DNA, dual incisions in the damaged strand, removal of the damage-containing oligonucleotide, repair synthesis in the resulting gap, and ligation of the repair patch to the contiguous parental DNA strand. These steps require the coordinated action of several factors and complexes, including the repair/transcription complex factor TFIIH, and the repair factors XPA, XPG, and excision repair cross-complementing rodent deficiency, complementation group 1 (ERCC1)-XPF, in addition to those required for repair replication and ligation.

The mismatch repair enzyme hMSH2 has also been linked to the NER pathway. This enzyme is a *TP53* target gene and induced by UVB radiation, suggesting a role for mismatch repair in skin cancer development (Rass & Reichrath, 2008).

Defects in NER are associated with three major autosomal recessive disorders, xeroderma pigmentosum (XP), Cockayne syndrome, and trichothiodystrophy. At the clinical level, XP is characterized by a highly increased incidence of tumours in sun-exposed areas of the skin (Stefanini & Kraemer, 2008). In contrast, Cockayne syndrome and trichothiodystrophy are cancer-free disorders characterized by developmental and neurological abnormalities and premature aging, associated in trichothiodystrophy with typical hair abnormalities (Lehmann, 2003). The two genes identified as responsible for the NER-defective form of Cockayne syndrome (*CSA* and *CSB*) are specifically involved in transcription-coupled repair TC-NER. Seven NER-deficient complementation groups have been identified in XP patients (designated XPA to XPG); these XP cases are defective in one of seven genes called *XPA* to *XPG*. An eighth complementation group, the so-called XP variant form (XPV) was latter identified with a defective gene encoding the DNA polymerase ε. This enzyme is required for the replication of the UV-damaged DNA pathway, called translesion DNA synthesis (Stefanini & Kraemer, 2008).

In addition, rare cases have been described showing a complex pathological phenotype with combined symptoms of XP, Cockayne syndrome and/or NER syndrome defects that have been associated with combinations of mutations in *XP*, *CS*, and other unidentified genes (for instance, Itoh *et al.*, 1994; Lehmann, 2003; Spivak, 2005; Nardo *et al.*, 2009).

The rarity of these syndromes associated with mutations in NER genes and compromised repair excludes a direct major public health impact on skin cancer risk, however, suboptimal NER capacity could also result in increased cancer risk. There is increasing evidence that more frequently found genetic variation such as SNPs can also impact on protein expression and function, and thus, potentially cancer risk. It is hypothesized that polymorphisms in genes implicated in the responses to the DNA damage and oxidative stress following exposure to UV constitute genetic susceptibility factors for skin cancers. This has been assessed in many molecular epidemiological studies using either a candidate gene approach or more recently genome-wide association studies (GWAS). SNPs in NER genes have been extensively investigated. For instance, for melanoma, significant associations were found for the NER genes *ERCC1* and *XPF* (which act together in a rate-limiting step in the repair pathway) in a study population of 596 Scottish melanoma patients and 441 population-based controls, with the strongest associations for melanoma cases aged 50 years and under (*ERCC1* OR, 1.59; 95%CI: 1.11–2.27, $P = 0.008$; *XPF* OR, 1.69; 95%CI: 1.18–2.43, $P = 0.003$)] (Povey *et al.*, 2007). Significant associations between melanoma and *XPD* SNPs have also been reported (e.g. Manuguerra, *et al.*, 2006). Variants in genes involved in the signalling cascades activated in response to UVR have been investigated. For instance the *TP53 Arg72Pro* polymorphism, but not *p73* G4C14 → A4T14 and *p21 Ser31Arg*, contribute to the risk of developing cutaneous melanoma (Li *et al.*, 2008).

Over the past few years several groups have assessed the DNA repair capacity in different populations in an attempt to identify "at-risk" subpopulations in the general population (Li *et al.*, 2009). Several DNA-repair phenotypic studies have been developed using cultured blood lymphocytes including the mutagen sensitivity assay, the host-cell reactivation assay, RT–PCR gene expression, microarray for protein expression, and DNA repair capacity. For instance, lower DNA repair capacity measured in a UV-based host-cell reactivation assay has been found in individuals with basal cell carcinoma and cutaneous melanoma (Li *et al.*, 2009), and increased mutagen sensitivity measured as *in vitro* UVB-induced chromatid breaks was found in basal cell carcinoma and squamous cell carcinoma patients (Wang *et al.*, 2005). The underlying molecular basis of this reduced repair capacity remains to be fully determined.

Several studies have reported an age-associated decline in NER (Moriwaki & Takahashi, 2008), which could result in an accumulation of damage, and reduced DNA-repair capacity has been found to be an independent risk factor for basal cell carcinoma and single or non-aggressive squamous cell carcinoma but not for multiple primaries, local aggressiveness, or recurrence of non-melanoma skin cancer (Wang *et al.*, 2007).

Differences have also been reported between keratinocytes and fibroblasts in terms of the lethal effects of UVB and oxidative stress, which could in part be explained by differences in repair capacity and the induction of apoptosis. Keratinocytes have a more efficient NER global genome repair (GGR) subpathway and are characterized by a strong anti-oxidant capacity and a higher susceptibility to reactive-oxygen-species-induced apoptosis than fibroblasts (D'Errico *et al.*, 2005; D'Errico *et al.*, 2007).

Studies following the persistence of DNA photoproducts using high-performance liquid chromatography coupled with tandem mass spectrometry have shown that the rate of removal of UVA-generated cyclobutane-pyrimidine dimers is lower than that of dimers produced by UVB irradiation in human skin using an in-vitro model system (Mouret *et al.*, 2006). The mechanistic basis of these differences in repair capacity remains unknown.

The base-excision repair and single-strand break repair pathways are the main routes for oxidative DNA damage. Attenuation of the repair of 8-oxoguanine via downregulation of the base-excision repair pathway results in hypersensitivity to UVA in a murine cell model (Kim *et al.*, 2002). In humans there is substantial inter-individual variation in 8-oxoguanine repair (Paz-Elizur *et al.*, 2007), and the presence of the *Ser326Cys* SNP in the human 8-oxoguanine DNA glycosylase (*hOGG1*) gene has been shown to impact on its constitutive activity, with the Cys variant protein having a lower enzymatic activity and a greater sensitivity to oxidative stress (Bravard *et al.*, 2009). UVA irradiation induces relocalization of the OGG1 to nuclear speckles where apurinic/apyrimidinic endonuclease-1 (APE1) is also found (Campalans *et al.*, 2007). APE1 is also known as redox factor-1 (REF-1), a redox regulator of multiple stress-inducible transcription factors such as nuclear factor–kappa B (NF-κB). Haploinsufficiency in mice of APE1 increases the apoptotic response to oxidative stress (Unnikrishnan *et al.*, 2009).

4.3.2 SNPs in genes other than those involved in DNA repair

The hypothesis that polymorphisms in genes implicated in the responses to the DNA damage and oxidative stress induced following exposure to UV constitute genetic susceptibility factors for skin cancers has been assessed in many molecular epidemiological studies using either a candidate gene approach or more recently GWAS. For instance, using in a GWAS of 930 Icelanders with basal cell carcinoma and 33117 controls, common variants on 1p36 and 1q42 were found

to be associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits (Stacey *et al.*, 2008). SNPs in immune-regulating components such as cytokines may lead to inter-individual differences in immunosuppression response and susceptibility to melanoma. For instance, in the interleukin-6 receptor gene (*IL-6R*), four SNPs (rs6684439, rs4845618, rs4845622, and rs8192284) in linkage disequilibrium were associated with an increased risk of melanoma (Gu *et al.*, 2008). An elevated risk of melanoma was observed in the heterozygous groups of these SNPs with odds ratios of 1.74 (95%CI: 1.07–2.81) for rs6684439; 1.72 (95%CI: 1.04–2.84) for rs4845618; 1.69 (95%CI: 1.03–2.75) for rs4845622; and 1.68 (95%CI: 1.04–2.73) for rs8192284. These associations were not observed in the homozygous variant group with odds ratios ranging from 0.93 to 1.03.

Associations have been found between polymorphisms in the promoter of the vitamin D receptor gene and malignant melanoma (Povey *et al.*, 2007; Barroso *et al.*, 2008; Mocellin & Nitti, 2008) and non-melanoma skin cancer (Gandini *et al.*, 2009).

There is some evidence for a contribution of pigmentation genetic variants, in addition to the melanocortin-1 receptor variants, to variation in human pigmentary phenotypes and possibly the development of skin cancer (Sturm, 2009). A first multistage GWAS of tanning response after exposure to sunlight in over 9000 men and women of European ancestry who live in the USA was recently reported (Nan *et al.*, 2009). An initial analysis of 528173 SNPs genotyped on 2287 women identified with LOC401937 (rs966321) on chromosome 1 as a novel locus highly associated with tanning ability. This association was confirmed in 870 women controls from a skin cancer case–control study with a joint *P* value of 1.6×10^{-9}. However this association was not replicated in two further studies. Several SNPs reaching the genome-wide significance level were located in or adjacent to the loci previously known as pigmentation genes: membrane-associated transporter protein gene (*MATP*), interferon regulatory factor 4 (*IRF4*), tyrosinase (*TYR*), blue eye oculocutaneous albinism type II (*OCA2*), and melanocortin-1 receptor (*MC1R*). These are similar to the hair-colour-related loci detected in the GWAS of hair colour (Han *et al.*, 2008).

4.4 Other effects

4.4.1 Immune response and photoadaptation

The development of skin cancer appears to be controlled in part by the immune system. Within the skin all the necessary cellular requirements are present to induce and elicit antitumoural immunity (Schröder *et al.*, 2006). Almost 30 years ago, Fisher and Kripke were the first to demonstrate that UVR caused suppression of certain aspects of the immune system (Fisher & Kripke, 1977). It has been well documented that patients with organ transplants that are maintained with immunotherapy are very prone to skin cancer (e.g. Bordea *et al.*, 2004). Immunosuppression by solar-simulated UV in men has been observed at doses three times lower than those required for immunosuppression in women (Damian *et al.*, 2008).

The major steps of UV-induced immune suppression have been determined but it should be noted that, in many instances, these details were obtained following a single or a few exposures of a rodent model or human subjects to UVR and that the dose chosen was sufficient to cause burning. In addition, the source used to emit UVR frequently contained more than 50% UVB (wavelength 280–315 nm), considerably more than natural sunlight. In experimental systems, there are differences between what is termed local and systemic immunosuppression. In the former, the antigen is applied directly to the irradiated body site soon after UV exposure. In the latter, following UV exposure of one part

of the body, the antigen is applied to a distant, non-irradiated body site (Applegate *et al.*, 1989).

Following UVB exposure, convincing evidence has been published to indicate that the chromophores for immunosuppression include DNA, urocanic acid (UCA), and cell membranes. Studies by Kripke's team were the first to suggest that DNA (and most likely, the pyrimidine dimer) may be the chromophore for UVB-induced immunosuppression (Applegate *et al.*, 1989), and evidence linking DNA damage with immune modulation has come from studies on XP patients (Suzuki *et al.*, 2001). *Trans*-UCA is a natural component of the strateum corneum, and UV induces a photoisomeric isomerization of *trans*-UCA to *cis*-UCA, which appears to be an initiator of the UV-immunosuppression, although its mechanism of action is still uncertain (Halliday & Rana, 2008; Norval *et al.*, 2008). UVA immunosuppression is likely to involve different chromophores than those required for UVB immunosuppression: molecules like porphyrins have been proposed (Halliday & Rana, 2008).

UVB irradiation triggers the production of various immunomodulatory mediators in the skin. These include cyclooxygenase-2 (COX-2), receptor activator of NF-κB ligand (RANKL), prostaglandins, platelet activating factor, histamine, neuropeptides and cytokines such as tumour necrosis factor (TNF) that modulate the reactivity of the immune cells in the skin (Beissert & Loser, 2008; Halliday & Rana, 2008; Norval *et al.*, 2008). For instance, TNF induces Langerhans cell activation and migration out of the skin into draining lymph nodes, thus limiting the capacity for antigen processing and presentation. Therefore, UVB ultimately suppresses the immune system by inducing the production of immunosuppressive mediators, by damaging and triggering the premature migration of antigen-presenting cells required to stimulate antigen-specific immune responses, by inducing the generation of suppressor cells and by inhibiting the activation of effector and memory T cells. Some of the mechanisms implicated in UVA-induced immunosuppression, such as increased COX-2 activity, are common to those observed after exposure to UVB. In addition, the production of reactive oxygen species and reactive nitrogen species by UVA alters the redox equilibrium and targets proteins, lipids and DNA, and modulates the immune cells resulting in aberrant behaviour and migration of antigen-presenting cells, the inhibition of T-cell activation, and generates suppressor cells (Norval, 2006; Norval *et al.*, 2008, Halliday & Rana, 2008).

The T helper1 (Th1) cytokine response is the main adaptive immune mechanism that offers protection from many infectious diseases. As UVR suppresses this preferentially, while promoting the Th2 cytokine response, there is the potential for UV exposure to increase the severity of infection, to alter viral oncogenicity, to cause reactivation from latency or to decrease the resistance to re-infection. Alteration of immune responses to microorganisms has been shown in rodent models following exposure to UVR (Norval, 2006). In humans, infections by herpes simplex virus (HSV) and human papilloma virus (HPV) are influenced by exposure to sunlight (see IARC, 2007b for details on UV and HPV). UVR is a recognized stimulus of HSV reactivation (Ichihashi *et al.*, 2004) through the suppression of the local immune response as a result of the UV exposure or a direct interaction between the UVR and the virus through modulation of the host transcription factors and the activation of HSV promoters, and hence reactivation of the virus.

There is also some evidence that there are genetic and other differences in the way that individuals respond to vaccination depending on UVR exposure (Norval, 2006). For instance, the findings from a meta-analysis of Bacille Calmette–Guérin clinical trials such as the increase of the efficacy of Bacille Calmette–Guérin vaccination with the

increasing distance from the equator suggested there might be an association between reduced vaccine efficacy and UVR (Colditz *et al.*, 1994).

Human and rodent skins have the capacity to adapt as a result of repeated suberythemal UV exposures. This photoadaption can attenuate the quantity of UVR that reaches the basal and suprabasal cells of the epidermis, and results in an enhanced ability to repair UV-induced DNA damage and an induction of protective enzymes such as superoxide dismutase. Whether photoadaption can lead to photoprotection against the normal downregulation of immunity induced by a high UV dose remains to be established as there are considerable gaps in the knowledge and there are many variables involved, including the acknowledged genetic diversity in the response of individuals to UVR. Evidence for the development of photoadaption is only apparent for epidermal DNA damage, no evidence exists when other parameters were considered such as total urocanic acid content or *cis* isomerization, Langerhans cells and dendritic cell numbers and function, natural killer cell numbers and function, dermal mast cell numbers or contact and delayed hypersensitivity responses (Norval *et al.*, 2008 and references therein). Thus, it is probable that repeatedly irradiating individuals with UVR is likely to continue to result in downregulation of immunity.

4.4.2 Modulation of gene expression

Differential gene expression in a variety of cell types has been demonstrated after exposure to different UV wavebands. For example Koch-Paiz *et al.* (2004) used cDNA microarrays to analyse the responses in human cell line MCF-7 cells following exposure to equitoxic doses of UVA, UVB, and UVC radiation. Under these experimental conditions, 310 of the 7684 genes on the array were UVB responsive, a subset of these to UVC and a subset of the UVB responsive genes also responsive to UVA.

Analysis of the UVR response genes in human melanocytes identified the tyrosine kinase ephrin receptor A2 (EPHA2) as an essential mediator of UVR-induced apoptosis (Zhang *et al.*, 2008).

Chronic UVR exposure can also modulate gene expression. For instance, chronic UVA radiation of human HaCaT keratinocytes results in decreased PTEN expression (He *et al.*, 2006).

MicroRNAs are very small endogenous RNA molecules about 22–25 nucleotides in length capable of post-transcriptional gene regulation. MicroRNAs bind to their target mRNA leading to cleavage or suppression of translation. MicroRNA profiles have been examined in melanomas (and melanoma cell lines) and Kaposi sarcoma (see Sand *et al.*, 2009 and table therein). For instance, the skin specific microRNA miR-203 that represses p63 expression, an important factor in epidermal cell proliferation and differentiation, is downregulated in melanoma lines; miR-221 and miR-222 are linked to melanoma progression through the downregulation of cyclin-dependent kinase inhibitor 1b (p27Kip1/CDKN1B) and the tyrosine kinase c-KIT receptor.

4.5 Synthesis

In addition to what is stated in the summary of Volume 55 of the *IARC Monographs*, it is now known that following exposure to the individual components of UVR, i.e. UVA, UVB or UVC, there is an overlapping profile of DNA damage detectable, in particular for cyclobutane-pyrimidine dimers. However, the proportion of different base-pair changes shows variation depending on the wavelength of radiation and cell type/species. The mechanisms leading to their formation may also be different. Recent experimental evidence in human cells shows that cyclobutane-pyrimidine dimers at cytosine-containing DNA sequences is formed following exposure to both UVA and UVB individually in human skin *ex vivo*.

Human cells have DNA-repair pathways that repair DNA photoproducts: the absence of

these enzymes, as seen in XP patients, leads to an increase risk of developing squamous cell carcinomas and melanomas lending support to a major role of DNA photoproducts in photocarcinogenesis.

UVR exposure gives rise to mutations in several genes in several human cell model systems, and mutations have been detected in several genes in human tumours, for example the *TP53* gene in squamous cell carcinoma and solar keratosis, at DNA bases where known photoproducts could have been formed lending support to a major role of DNA photoproducts in photocarcinogenesis.

Mutations can be detected in human cells exposed to UVA, UVB and UVC: the base-pair changes involved in some of these mutations overlap. In particular, mutations found involving C→T transitions are found in cells treated with either UVA, UVB or UVC. The same situation is found when the base-pair changes, for instance in the *TP53* gene, are analysed in human squamous cell carcinoma and solar keratosis. As C→T transitions are not a specific "fingerprint" for UVA, UVB or UVC, either radiation type could have been at the origin of the exposure initiating the carcinogenic process.

Based on the above mechanistic considerations, UVA, UVB and UVC are carcinogenic in human cells.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma, squamous cell carcinoma of the skin and basal cell carcinoma of the skin. A positive association has been observed between exposure to solar radiation and cancer of the lip, conjunctival squamous cell carcinoma and ocular melanoma, based primarily on results observed in the choroid and the ciliary body of the eye.

There is *sufficient evidence* in humans for the carcinogenicity of the use of UV-emitting tanning devices. UV-emitting tanning devices cause cutaneous malignant melanoma and ocular melanoma (observed in the choroid and the ciliary body of the eye). A positive association has been observed between the use of UV-emitting tanning devices and squamous cell carcinoma of the skin.

There is *sufficient evidence* in humans for the carcinogenicity of welding. Current evidence establishes a causal association for ocular melanoma although it is not possible without a full review of welding to attribute the occurrence of ocular melanoma to UV radiation specifically.

There is *sufficient evidence* in experimental animals for the carcinogenicity of solar radiation, broad-spectrum UVR, UVA radiation, UVB radiation, UVC radiation.

Solar radiation is *carcinogenic to humans (Group 1).*

Use of UV-emitting tanning devices is *carcinogenic to humans (Group 1).*

Ultraviolet radiation (bandwidth 100–400 nm, encompassing UVC, UVB and UVA) is *carcinogenic to humans (Group 1).*

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X- AND γ-RADIATION

X-and γ-radiation were considered by a previous IARC Working Group in 1999 (IARC, 2000). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Physical properties

Radiation sources can be either external to the body, such as medical X-rays, or through deposition on the Earth's surface, or internal. Internal exposure can result from the ingestion of contaminated foods, inhalation, dermal absorption, or injection of radionuclides. The effects of radiation are directly related to the dose that an organ receives, and any differences between the effects of external and internal sources is in large part related to the distribution of dose within and among body organs (IARC, 2001).

The activity of a radionuclide is defined as the number of nuclear transformations occurring per unit of time. The standard unit is the becquerel (Bq), which is 1 disintegration per second. Historically, the curie (Ci) (1 Ci = 3.7×10^{10} Bq) was also used. The energy of radiation emitted during the nuclear transformation is normally measured in units of electron-volts (eV), as this is a small unit, it is commonly represented as kilo eV (keV) (1000 eV) or mega eV (MeV) (10^6 eV).

1.1.1 X- and γ-rays

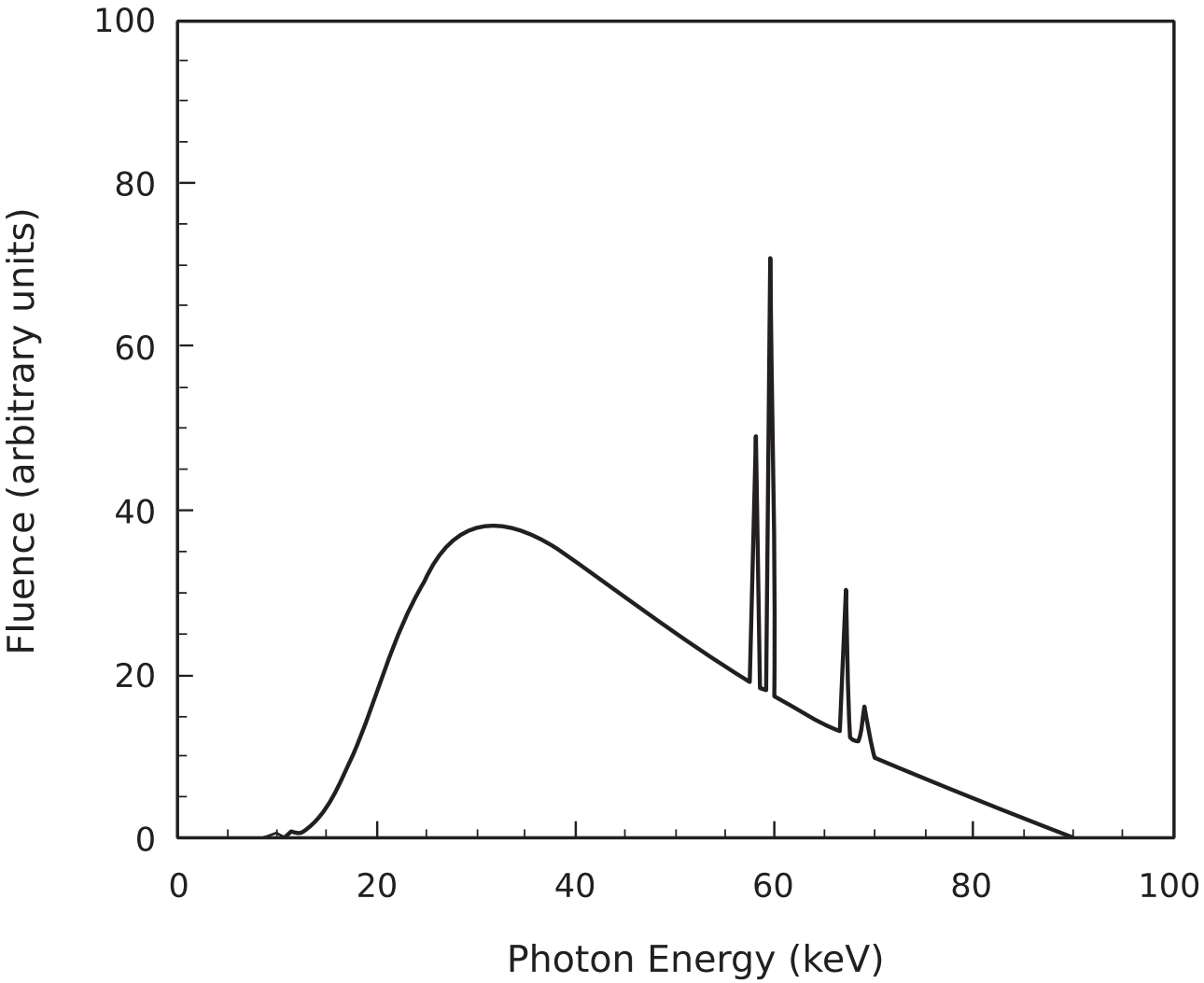
X- and γ-rays are both electromagnetic radiations distinguished mainly by their origin. X-rays are photons emitted from the electron shells surrounding the atomic nucleus or during the slowing down of electrons or other charged particles. The term γ-rays is usually applied to radiation originating from the atomic nucleus, and from particle annihilation. The energy ranges of X- and γ-rays overlap considerably with X-rays having energies upwards from a few tens of eV (the shortest ultraviolet wavelengths), and γ-ray energies extending up to a few tens of MeV.

(a) X-rays

Characteristic X-rays are emitted during transitions of electrons in excited atomic shells to lower energy states: they have line spectra characteristic of the corresponding element. A continuous X-ray spectrum is produced when charged particles, normally electrons, are decelerated or deflected (in an electric or magnetic field such as that close to a nucleus). This is known as 'bremsstrahlung' from the German for 'braking radiation'.

For example, X-ray tubes generate bremsstrahlung and characteristic X-rays (see Fig. 1.1). X-rays for medical exposures are classified,

Fig. 1.1 Bremsstrahlung X-ray spectrum from a tungsten target at 90 kVp with 1 mm aluminium filtration. The peaks between 57 and 70 keV are due to characteristic X-rays of tungsten



Adapted from IPEM (1997)

according to their kVp (the peak applied voltage for an exposure) from ultrasoft (5–20 kVp), to very hard (> 250 kVp). Extremely hard X-rays are generated with betatrons, synchrotrons, and linear accelerators in the MeV range.

X-rays are used in many medical and technical applications. The most common are diagnostic X-ray examinations of the human body, and the analysis of materials. In X-ray therapy, the biological effect of X-rays is used to destroy malignant tissue. It is applied mainly to treat cancer patients, when high doses are delivered to a limited area of the body, with restricted irradiation of adjacent tissue (IARC, 2000).

(b) γ-Rays

γ-Ray photons are usually emitted during transformations in atomic nuclei. They have widely different energies in the range of 0.01–17.6 MeV. Such radiation can also be produced by the decay of elementary particles, the annihilation of electron–positron pairs, and the acceleration and deceleration of high-energy electrons in

cosmic magnetic fields or in elementary particle accelerators.

1.1.2 Neutrons

Neutrons are uncharged particles which, along with protons, form the nuclei of atoms. Whereas X- and γ-rays interact primarily with orbital electrons, neutrons interact with the nucleus of atoms. Neutrons are emitted from nuclei in several ways, in the interaction of high-energy cosmic radiation with the Earth's atmosphere, and in the fission or fusion of nuclei. Fission neutrons have energies up to several MeV, and fusion neutrons approximately 10 MeV. Neutrons can also be produced by the collision of energetic charged particles (e.g. α-particles, ions from an accelerator) with a suitable target material. The neutrons emitted are used for radiography and radiotherapy.

1.1.3 α-particles

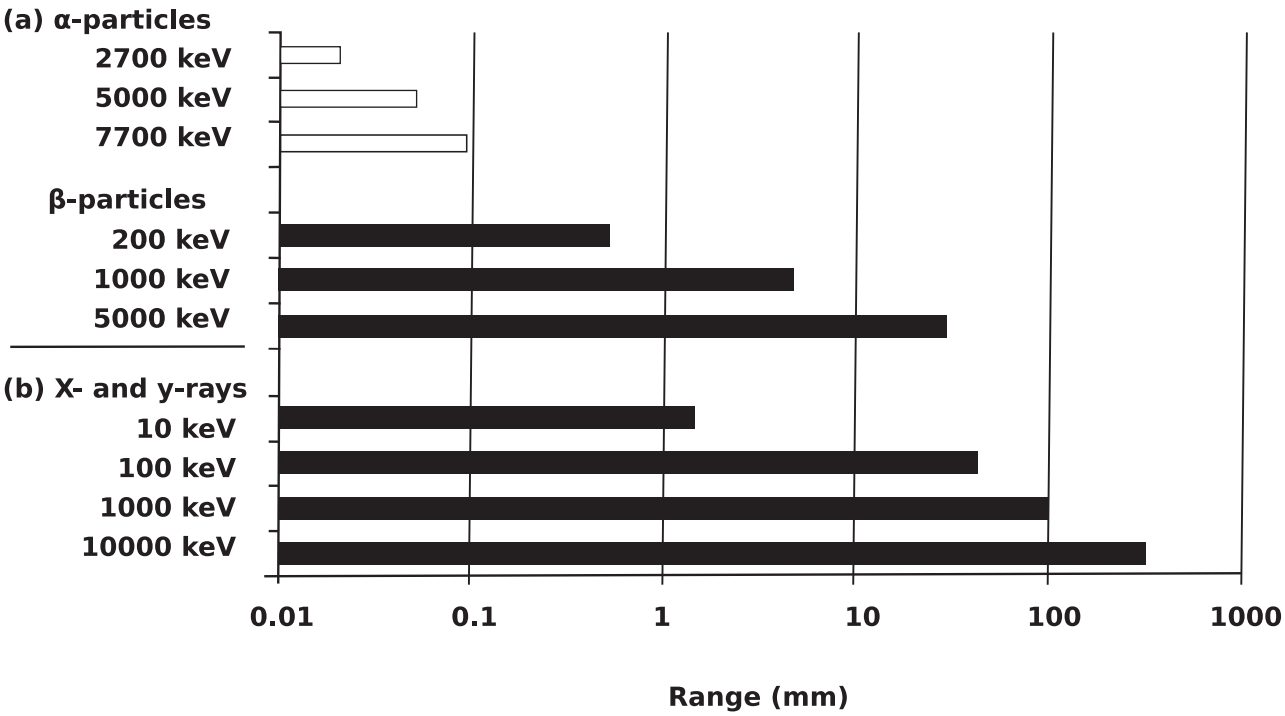
α-particles are emitted from the nucleus of a radionuclide and consist of two protons, giving them a +2 charge, and two neutrons bound together, resulting in an atomic mass of 4, so they are, in effect, high energy helium-4 (^{4}He) atome The energy of α-particles typically varies between 4 and 8 MeV, the energy increasing with the mass of the parent nucleus which emitted it. Consequently, emissions from any particular radionuclide are mono-energetic and have a characteristic energy. Because the energy and mass of an α-particle are significant on an atomic scale, the emission of an α-particle causes the parent/daughter nucleus to recoil. This α-recoil effect represents a small, but not negligible, percentage (~2%) of the overall energy released during α decay. α-particles rapidly lose energy and acquire electrons from the surrounding environment to become inert Helium-4 (their typical lifetime is a few picoseconds).

1.1.4 β-Particles

β-Particles are emitted from the nucleus of a radionuclide and consist of electrons or anti-electrons, these electrons have a mass of approximately 0.00055 of an atomic mass unit. β^- (negatron) radiation is the result of the conversion of a neutron into a proton, a negatively charged electron being emitted as a result. β^+ (positron) radiation is a result of the opposite conversion, a proton is converted to a neutron and an anti-electron, the positively charged equivalent of an electron, known as a positron, is emitted. β radiation also results in the production of a third body, the first two bodies being the daughter nuclide and the electron/positron. The third body is an anti-neutrino in the case of β^- emission and a neutrino in the case of β^+ emission. Because the energy from β radiation is shared between the emitted particle and the third body, the energy of β-particles varies, even when the parent radionuclide is the same (i.e. their energy is not characteristic). The continuum of energies for a β-particle goes from a lower energy limit of zero to an upper limit set by the maximum available energy from the transmutation of the parent into the daughter (the reaction energy 'Q', typically around 1 MeV). Many β emitters also emit γ-rays, those that do not are known as 'pure' β emitters. High-energy β-particles can produce bremsstrahlung. Emitted β^- particles quickly (in a few tens of picoseconds) lose their excess energy, and are then indistinguishable from other electrons in the environment. As positrons are anti-electrons, they are normally rapidly annihilated after they are emitted as a result of collisions with electrons in the surrounding environment, which are also annihilated. The released energy manifests itself as two characteristic 0.511 MeV γ-rays.

For the sake of clarity, β^- particles will henceforth be referred to as β-particles and β^+ particles as positrons.

Fig. 1.2 (a) Depth of penetration of α and β-particles in tissue, for selected energy values; (b) depth of penetration of X- and γ-rays in tissue in which 50% of the radiation energy is lost



From IARC (2000)

1.2 Interactions with matter

Different radiation types penetrate matter to a different extent and in different ways (Fig. 1.2). X- and γ-rays, especially those with high energy, can penetrate matter easily, while α- and β-particles are much less penetrating.

Ultimately, virtually all the radiation energy from ionizing radiation is transferred to electrons, which lose their energy by ionizing the irradiated medium.

For radiation protection purposes, the International Committee for Radiation Protection (ICRP, 2007) introduced radiation-weighting factors to take into account the fact the various radiation types have different relative biological effects (RBE). The primary dosimetric quantity unit of dose taking radiation-weighting factors into account is the sievert (Sv), which should be used with caution (note that values of radiation-weighting factors have changed over the years). For epidemiological purposes, the basic physics quantity of the gray (Gy, i.e. joule per kilogram) should be used where possible. For X- and γ-rays, the radiation-weighting factor has always been 1, and values for individual organs could therefore equally well be expressed in terms of absorbed dose in grays or equivalent dose in sieverts.

Doses may be expressed in terms of effective (whole-body equivalent) dose (ICRP, 2007). Effective doses should only be used for radiation protection and regulatory purposes, and with caution for general comparisons.

1.2.1 X- and γ-rays

The interaction of X- and γ-rays with matter is described by the photoelectric effect, Compton scattering, and pair production. Photoelectric

absorption dominates at low energies followed by Compton scattering, and then pair production as the energy increases. Absorption of very high energy photons results in nuclear disintegration. The intensity of X- and γ-rays generally decreases with depth. The ability to penetrate matter increases with increasing energy and decreases with increasing atomic number of the absorbing material.

The above processes (apart from photodisintegration) all result in the production of electrons (or their anti-matter equivalent, positrons) and lower energy X-rays, which undergo further absorption and scattering. The energy of the initial photon is thus transferred to electrons that create ionization leading to significant chemical and biological effects such as degradation of DNA.

1.2.2 Neutrons

Neutrons are captured or scattered by matter. The likelihood of interactions occurring between neutrons and atoms of a material (i.e. the neutron cross-section) is unique for each nuclide, and the nature of these interactions are complex. Thermal neutron-capture cross-sections are generally much greater than those at higher energies: in nuclear power reactors, neutron energies must be reduced by collisions with a moderating medium (usually water or graphite) to thermal energies where the cross-sections allow a chain reaction to proceed.

The mean free path of neutrons in tissues varies with their energy from a fraction of, to several tens of centimetres. In tissue, neutrons interact with hydrogen nuclei. The recoiling nuclei (low-energy proton) form densely ionizing tracks, with a high linear energy transfer (LET) which are efficient in producing biological injury. The ICRP (2007) has therefore defined radiation-weighting factors for estimating the risks associated with exposure to neutrons, which are larger than those for X- or γ-rays for the same tissue dose.

In tissue, neutrons with energy > 50 MeV interact mainly with nuclei such as C, N, O, and Ca, producing many lower energy particles such as α-particles, protons, and other neutrons with a broad distribution of LET. Exposure to high-energy neutrons is thus quite distinct from exposure to low-energy neutrons. Neutrons as they interact with matter generate γ-rays.

1.2.3 α and β Radiation

Charged particle radiation, such as α and β radiation, is not very penetrating, the maximum range of an α-particle in tissue is less than 100 microns and for β-particles only about a centimetre. This means that, for external exposures, these types of radiation are often a much lower or, in the case of α-particles, insignificant radiological hazard when compared to highly penetrating radiation such as X- and γ-rays. However, when α- and β-particle emitters become internally deposited within living tissues, their radiations deposit most, if not all, of their energy within that tissue. α-particles in particular are relatively massive, doubly charged, and very densely ionizing. Consequently, they have a substantially enhanced effect on living tissues per unit energy, compared to X- and γ-rays, and β-particles. There is also some evidence, from radionuclides such as tritium, that β-particle radiation may have a slightly greater radiological effect per unit energy than X- and γ-rays.

Neutrinos and anti-neutrinos interact very weakly with matter, therefore present no radiological hazard, and will not be considered further.

1.2.4 Others

Other types of ionizing radiation that interact with matter include cosmic rays, protons, muons, and heavy ions. As for the other forms of radiation described above, these will all ultimately produce ionizing electrons.

1.2.5 Energy loss process

As described above, the indirectly ionizing radiations all interact to produce ionizing particles; electrons, protons, α–particles, and heavy ions.

All ionizing particles interact with the atomic electrons of the medium through which they pass to produce secondary electrons with a range of energies. In turn, these electrons create more electrons (mainly low energy) until all electrons are completely slowed down in the medium. At the end of their tracks, electrons of less than about 500 eV form clusters of ionization. An analysis of low-energy electron track structure in liquid water is given by Wilson *et al.* (2004).

1.2.6 Radionuclides, internally deposited

For the purposes of this *IARC Monograph*, internally deposited radionuclides are defined as radionuclides that have been taken into the body (encapsulated radionuclides entering the body, as in brachytherapy, are not discussed in this *Monograph* because they are considered as external exposure). These radionuclides may emit any form of radiation, but in practice it is those that emit charged particles, α (α) and β (β^-)/(β^+) radiation, that tend to be the most radiologically significant.

In theory, any radionuclide could become internally deposited but only a subset of radionuclides which are relatively available from nuclear weapons tests, the Chernobyl accident, or from radiotherapy and radiodiagnosis, and known to have the potential to affect cancer risks are considered here. To understand the occurrence of radionuclides within the environment and their potential to result in significant individual exposures, it is necessary to have some knowledge of their physical and chemical properties as well as their abundance—this information has been collated from various sources: The CRC 'Handbook of Chemistry and Physics' (Lide, 2005–2006), World Nuclear Association Reference Documents 'Radiological and Chemical Fact Sheets to Support Health Risk Analyses for Contaminated Areas' (Argonne National Laboratory, 2007) and ICRP (1983, 2008). The information provided is not intended to be definitive or comprehensive.

(a) Tritium

Tritium (^{3}H) is an isotope of the hydrogen atom. ^{3}H is naturally produced by interactions between cosmic radiation and nitrogen and oxygen in the atmosphere at a rate of approximately 0.4 kg/year. However, environmental concentrations of naturally occurring ^{3}H are low (the total steady-state global inventory from this route of production is ~7 kg) due to global dispersal, and because they are constantly being depleted by radioactive decay as a result of its comparatively short half-life. ^{3}H gas will tend to bond with any available moisture to form tritiated water, which, from a biochemical perspective, behaves like any other water in the environment.

^{3}H is a pure, low energy, β emitter that has a half-life of 12.35 years, it decays to helium-3, which is stable.

Although ^{3}H is not a particularly abundant fission product (uranium-235 fission yield is 0.01%) and the atmospheric testing of nuclear weapons has largely ceased, the quantity of ^{3}H in the environment from previous tests still exceeds that from natural cosmogenic production. However, once again due to global dispersal of this material, concentrations involved are low.

^{3}H is a strategic material in the production of nuclear weapons; and because of the nature of this application, specific information on the amounts of ^{3}H generated and used for this purpose are difficult to obtain. Production of ^{3}H for weapon purposes involves neutron bombardment of lithium-6 in nuclear reactors. The ^{6}Li atom, with three protons and three neutrons and the captured neutron combine to form a lithium-7 atom, with three protons and four neutrons,

which instantaneously splits to an atom of ^{3}H (one proton and two neutrons) and one atom of ^{4}He (two protons and two neutrons). The United States of America is thought to have produced over 200 kg of ^{3}H for military purposes but much of this has now decayed to ^{3}He, and only ~75 kg remains (Argonne National Laboratory, 2007).

Heavy water ($^{2}H_2O$) moderated reactors, such as the CANada Deuterium Uranium (CANDU) designs, produce substantial amounts of ^{3}H as a by-product, due to neutron capture in the moderator. ^{3}H is routinely removed from the heavy water used in CANDU reactors in Canada, and approximately 1–2 kg are recovered per year.

^{3}H can be produced in a particle accelerator by bombarding ^{3}He with neutrons. In addition, ^{3}H is used in the manufacture of radionuclide-labelled materials for application in medicine, research and industry (and can be released from such manufacturing plants), and in the use and disposal of these materials. ^{3}H has also been used in luminous paint used in some wristwatches and compasses, and in emergency exit signs, and gun-sights (HPA, 2007).

(b) Phosphorus-32

Phosphorus is an abundant, naturally occurring, reactive non-metal, and is never found in its elemental form in the environment. Compounds containing phosphorus are essential to life and are involved in many metabolic processes. Only one phosphorus isotope is not radioactive, ^{31}P, and this is the only isotope found in nature.

^{32}P is a man-made isotope, generally used for medical purposes. It is produced by neutron bombardment of sulfur-32 (^{32}S, this involves a 'n,p' reaction, where a neutron is captured and a proton is ejected), is a pure β particle emitter with a half-life of 14.29 days, and decays back to ^{32}S, which is stable. Because of its short radioactive half-life ^{32}P must be used relatively quickly after it is produced, and it cannot be stockpiled.

(c) Strontium-90

Strontium is a relatively abundant, chemically reactive metal, which oxidizes readily. Naturally occurring strontium has four stable isotopes ^{84}Sr, ^{86}Sr, ^{87}Sr, and ^{88}Sr. The chemistry of strontium has similarities to that of calcium.

^{90}Sr is a man-made isotope that is a pure β particle emitter with a half-life of 29.12 years. It decays to Yttrium-90, which is a short-lived high energy β particle emitter, which greatly increases the radiological effect of ^{90}Sr exposures. ^{90}Sr is mostly produced as a result of nuclear fission, either in nuclear weapons or batteries/reactors, and is one of the most commonly occurring fission products (^{235}U fission yield is ~6%). Its relatively long half-life results in it being persistent in the environment if it is released. Levels of ^{90}Sr in surface soil due to fallout from atmospheric nuclear weapons tests are around 3.7 Bq/kg on average.

(d) Iodine-131

Iodine is a halogen, it is both volatile and reactive, and is not found in its elemental form in nature but rather, most commonly, as iodide ions. Only one isotope of iodine is stable, ^{127}I. Iodine is an essential element and the human body contains about 20 mg mainly in the thyroid gland.

^{131}I is a man-made isotope that is a β and γ emitter with a short half-life of 8.04 days. It decays to xenon-131, a small percentage to its metastable state, which is a γ emitter, but mostly (~99%) to its ground state, which is stable.

As it is a common fission product (^{235}U fission yield is ~3%), ^{131}I is produced by nuclear weapons and in nuclear batteries/reactors. Because it is volatile, ^{131}I can more readily escape from containment than other fission products, but its relatively short half-life means it does not persist in the environment for long periods.

^{131}I is also produced via neutron bombardment of tellurium-130 for medical diagnostic and

treatment purposes. Because of its short half-life, it cannot be stockpiled for this purpose. Global demand for ^{131}I for medical purposes is approximately 600 tera (T)Bq (600 × 10^{12} Bq).

(e) Caesium-137

Caesium is a rare naturally occurring, highly reactive alkali metal with only one stable isotope ^{133}Cs. The chemistry of caesium has some similarities to that of potassium.

^{137}Cs is a man-made isotope that is a β and γ emitter with a half life of 30 years. It decays to barium-137, mostly (~95%) to its metastable state, which is a short-lived energetic gamma emitter, but also to its ground state, which is stable. ^{137}Cs is mostly produced as a result of nuclear fission, either in nuclear weapons or batteries/reactors, and is one of the most commonly occurring fission products (^{235}U fission yield is ~6%). Its relatively long half-life results in it being persistent in the environment if released. Levels of ^{137}Cs in surface soil due to fallout from atmospheric nuclear weapons tests are around 15 Bq/kg on average.

(f) Radon

Radon is a noble (chemically inert) gas mostly produced through the radioactive decay of environmental uranium/thorium and their radioactive daughters. All of the isotopes of radon are radioactive: ^{222}Rn is the isotope with the longest radioactive half-life, and its naturally abundant parent is ^{226}Ra, itself a daughter of ^{238}U (see Fig. 1.3), ^{222}Rn is the most prevalent in the environment. ^{220}Rn (also known as thoron) is the only other isotope of radon that is found in any significant quantity in nature. That isotope and its radioactive daughters typically contribute less than 20% of the total dose from radon, and its contribution is often not included in radon exposure assessments. Henceforth, the term radon should be taken as referring to Radon-222 unless otherwise indicated.

^{222}Rn is an α-particle emitter with a short half-life of 3.82 days, it decays to polonium-218, which is also an α-emitter, and has in turn further short-lived radioactive daughter products (see Fig. 1.3). The presence of this decay chain greatly increases the overall radiological significance of this isotope. Although ^{222}Rn is a gas, its short-lived progeny are electrically charged particles that can become attached to environmental dust particles in the air, the existence and extent of this 'attached' fraction has a considerable impact on dose to the upper airways of the lung.

Like its parent radiosotopes (see Fig. 1.3), ^{222}Rn is omnipresent in nature but levels vary because certain types of rocks and soils (e.g. granite, phosphate rocks, and alum shales) contain more of its parents than others (Appleton, 2007). ^{222}Rn rapidly disperses into the troposphere when it escapes into the free atmosphere, i.e. outside of enclosed spaces. Consequently, concentrations of ^{222}Rn in breathing air in open spaces is relatively low, typically around 10 Bq/m^3.

^{222}Rn can also be found in building materials albeit at low concentrations (de Jong *et al.*, 2006). Building materials such as concrete, wallboard, brick and tile usually have concentrations similar to those of major rock types used for their manufacture, and levels also vary according to the type of rock used for construction (Mustonen, 1984; Ackers *et al.*, 1985). Although building materials generally contribute only a very small percentage of the indoor air ^{222}Rn concentrations, in a few areas, concrete, blocks, or wallboard incorporating radioactive shale or waste products from uranium mining can make an important contribution to the indoor ^{222}Rn levels (Man & Yeung, 1998; Åkerblom *et al.*, 2005).

(g) Radium

Radium is a naturally occurring rare earth metal. Ubiquitous in the environment, in small quantities, it is found in soils, uranium/thorium ores (e.g. pitchblende), minerals, ground water, and seawater, because the common radium

Fig. 1.3 Uranium-238 decay chain

Radionuclide	Half-life
Uranium-238	4,468,000,000 years
↓ α-particle	
Thorium-234	24.1 days
↓ β-particle	
Protactinium-234m	1.17 minutes
↓ β-particle	
Uranium-234	2,444,500 years
↓ α-particle	
Thorium-230	75,400 years
↓ α-particle	
Radium-226	1,600 years
↓ α-particle	
Radon-222	3.82 days
↓ α-particle	
Polonium-218	3.11 minutes
↓ α-particle	
Lead-214	26.8 minutes
↓ β-particle	
Bismuth-214	19.9 minutes
↓ β-particle	
Polonium-214	0.000163 seconds
↓ α-particle	
Lead-210	22.3 years
↓ β-particle	
Bismuth-210	5.01 days
↓ β-particle	
Polonium-210	138 days
↓ α-particle	
Lead-206	**Stable**

isotopes are products of the main uranium/thorium decay chains. All the isotopes of radium are radioactive, ^{226}Ra has the longest half-life, and therefore is the predominant isotope found in nature.

^{226}Ra is an α-particle emitter with a half-life of 1600 years, and decays to ^{222}Rn, which is also an α-particle emitter.

^{228}Ra is a β and gamma emitter with a half-life of 5.75 years, and decays to actinium-228, which is a β-particle and gamma emitter.

^{226}Ra concentrations in soil vary considerably, typically between 10–50 Bq/kg, with approximately 25 Bq/kg considered to be average (UNSCEAR, 1982), concentration in seawater is 4–5 orders of magnitude lower than this.

^{223}Ra and ^{224}Ra are both α-particle emitters with a half-life of 11.43 days and 3.6 days, respectively. ^{224}Ra can be found in ground water.

(h) Thorium-232

Thorium is a naturally occurring dense metal that is usually found in minerals such as monazite, thorite, and thorianite. Thorium is thought to be about three times more abundant than uranium in the environment. All of the isotopes of thorium are radioactive, therefore the isotope with the longest radioactive half-life, ^{232}Th, is by far the most prevalent in nature.

^{232}Th is an α-particle emitter with a half-life of 1.41×10^{10} years, and decays to ^{228}Ra, which is a β-particle emitter.

^{230}Th is present in soil and ores with ^{232}Th. ^{230}Th is a decay product of ^{234}U. ^{230}Th is an α-particle emitter with a half-life of 7.54×10^{4} years.

(i) Uranium

Uranium is a naturally occurring very dense metal, which is widespread in the environment, including seawater, at low concentrations. All of the isotopes of uranium are radioactive, therefore the isotopes with the longest radioactive half-lives are the most prevalent in nature. Environmental uranium is made up of three

isotopes: ^{234}U, ^{235}U, and ^{238}U. ^{238}U is predominant by mass at 99.284%; ^{235}U, accounting for 0.711%; and, ^{234}U only 0.005% (it should be noted that natural isotopic composition can vary slightly).

^{234}U is an α-particle emitter with a half-life of 2.445×10^5 years, and decays to ^{230}Th, which is also an α-particle emitter.

^{235}U is an α-particle and gamma emitter with a half-life of 7.03×10^8 years, and decays to ^{231}Th, which is a β-particle and gamma emitter.

^{238}U is an α-particle emitter with a half-life of 4.468×10^9 years, and decays to ^{234}Th, which is a β-particle and gamma emitter.

Of the three naturally occurring uranium isotopes, only ^{235}U has the capacity to support sustained nuclear fission through a chain reaction. Hence, uranium is commonly classified into types depending on the percentage of ^{235}U it contains, as compared to that in naturally occurring uranium ores (0.711% by mass). Natural uranium, as its name would suggest, has the same percentage of ^{235}U as uranium ores. Depleted uranium, which is a common by-product of the nuclear fuel cycle, has a lower percentage of ^{235}U than natural uranium. Enriched uranium typically contains about 2.5–3.5% by mass of ^{235}U, and is widely produced on an industrial scale for use in the manufacture of power reactor fuel assemblies. Highly enriched uranium is almost all ^{235}U, greater than 80% by mass, and is produced in much more limited quantities than normal enriched uranium for use in nuclear propulsion reactor systems, and for nuclear weapons.

Approximately 50000 tonnes of natural uranium are mined annually, about more than half of this amount is produced by mines in Kazakhstan, Canada, and Australia with the remainder coming from mines in many countries throughout the world.

World stockpiles of depleted uranium are currently more than 1 million tonnes, with over 50000 tonnes being added per year.

Approximately 60000 tonnes of enriched uranium is produced for nuclear fuel production purposes annually by facilities in the USA, Canada, France, the Russian Federation, and the United Kingdom.

A total of over 2000 tonnes of highly enriched uranium are though to have been produced for military purposes (World Nuclear Association, 2009).

(j) Plutonium

Plutonium is a man-made (predominantly), very dense, rare earth metal, which has a complex chemistry. All the isotopes of plutonium are radioactive, the most commonly occurring isotopes are the α-particle emitters ^{239}Pu, ^{240}Pu and, increasingly, the β-particle emitter, ^{241}Pu. Shortly after its discovery, ^{239}Pu was identified as a strategic material for nuclear weapons production, because it has the capacity (greater than that of ^{235}U) to support sustained nuclear fission. Most of the plutonium now in existence has been man-made as a result of nuclear weapons and power production programmes. However, small quantities of plutonium have also been found at the site of the so-called 'natural reactor' at Oklo in Gabon West Africa. ^{239}Pu is produced through neutron capture by ^{238}U, within nuclear batteries/reactors. This yields ^{239}U which decays to ^{239}Np by β-particle emission, which decays further to ^{239}Pu, also by β-particle emission. The longer that nuclear fuel is used ('burned') in a reactor, the greater the number of plutonium isotopes that appear in increasing quantities, e.g. neutron capture by ^{239}Pu yields ^{240}Pu, which can, in turn, capture neutrons to produce ^{241}Pu. ^{238}Pu is also increasingly produced from ^{235}U through neutron-capture reactions and radioactive decay.

^{238}Pu is a high-energy α-particle emitter with a half-life of 88 years, and decays to ^{234}U, which is also an α-particle emitter.

^{239}Pu is an α-particle emitter with a half-life of 24065 years, and decays to ^{235}U, which is also an α-particle emitter.

^{240}Pu is an α-particle emitter with a half-life of 6500 years, and decays to ^{236}U, which is also an α-particle emitter.

^{241}Pu is primarily a β-particle emitter with a half-life of 14 years, and decays to ^{241}Am, which is a radiologically significant α-particle emitter.

The only plutonium isotope required for nuclear weapons purposes is ^{239}Pu, and the presence of other isotopes of plutonium, such as ^{240}Pu, can also be a hindrance to this application. Therefore, plutonium is classified into different grades depending on its ^{239}Pu and ^{240}Pu content. The primary distinction is between weapons-grade material, which is more than 93% ^{239}Pu, and other grades, for example reactor grade, which contain lower percentages of ^{239}Pu.

Because of the secrecy surrounding nuclear weapons, precise figures on weapons-grade plutonium production are difficult to obtain, however, total worldwide production is thought to have been of the order of several hundred tonnes. Global stockpiles of weapons-grade plutonium have diminished as a result of strategic arms limitation agreements, and are currently believed to be about 250 tonnes.

Approximately 70 tonnes of reactor-grade plutonium are produced by power-generating nuclear reactors every year, this adds to an existing inventory of about 1300 tonnes globally, much of this is still contained in spent fuel (World Nuclear Association, 2009).

^{238}Pu is used as a heat source in radiothermal generators to produce electricity for a variety of purposes (Argonne National Laboratory, 2007).

1.3 Exposure

1.3.1 X-rays, γ-rays and neutrons

Detailed information on the different methods of measurement (present and historical) of all types of external radiation and their associated uncertainty can be found in NCRP (2007). Estimates of neutron dose are uncertain because good personal neutron dosimetry is difficult to achieve over all energy ranges (energies of importance cover a range > 10^9 eV), and detection thresholds are often high, particularly in the early days of monitoring.

(a) Accidents

The production and transport of nuclear weapons have resulted in several accidents. The two most serious accidents in nuclear weapons production were at the Mayak complex near Kyshtym in the Russian Federation (formerly the Soviet Union), and at the Windscale plant at Sellafield in the United Kingdom. A major accident in a nuclear power plant occurred in Chernobyl, Ukraine.

(i) Southern urals

Mayak, the former Soviet Union's main production facility for weapons-grade plutonium was built near the town of Ozersk in the southern urals, the Russian Federation, in the 1940s. Operations at this facility resulted in several major, and persistent minor, uncontrolled releases of activity into the surrounding environment, particularly the Techa river.

In 1957, a Mayak waste storage facility located near Kyshtym exploded as a result of a chemical reaction, this incident is referred to as the Kyshtym accident. The region contaminated by this accident had a population of approximately 273000 people and around 11000 of these had to be relocated, including 1500 people who had previously been resettled from the Techa River area. In Mayak, the total collective effective dose to an exposed population of 273000 was 2500 man.Sv (UNSCEAR, 2000a). This and other discharges from the plant (routine and accidental) resulted in substantial doses to workers (see Vasilenko *et al.*, 2007) and to the local population (Degteva *et al.*, 2006).

As a result of a drought in 1967, Karachay Lake, which had been used as an open depot for liquid radioactive waste from Mayak, dried

up and the winds associated with a subsequent storm picked up radionuclide-loaded sediments from the lake and distributed them over a wide area.

(ii) Windscale fire

In October 1957, at the Windscale Works, now part of the Sellafield site, in the United Kingdom, a nuclear reactor used to produce plutonium for weapons caught fire. Before the fire could be extinguished, damage occurred to the irradiated fuel contained in the reactor, and radionuclides were released in the environment. Because of the design of this reactor, which incorporated the filtration of exhausted coolant air, mainly gaseous and volatile radioisotopes escaped. In the Windscale accident, doses were mainly due to internal ingestion, and are reported in Section 1.3.

(iii) Three Mile Island

Failure to maintain coolant fluid in a commercial light-water reactor at Three Mile Island in the USA resulted in the reactor core becoming exposed to the air, and led to a partial meltdown of the fuel load.

(iv) Chernobyl

In the accident at Chernobyl in the Ukraine in April 1986, a Russian reactor Bolshoy Moschnosti Kanalniy (RMBK) became uncontrollable creating a steam explosion and a subsequent fire, which resulted in a loss of containment and ultimately to the complete destruction of the reactor. In the Chernobyl accident, the main contributor to the dose from external irradiation was ^{137}Cs. The doses to individuals throughout the northern hemisphere varied widely, some staff and rescue workers on duty during the accident receiving fatal doses > 4 Sv (Savkin *et al.*, 1996). Yearly averaged doses to operation recovery workers of Belarus, the Russian Federation, and Ukraine were in the range of 20–185 mGy during 1986–89 (UNSCEAR, 2008a).

(b) External exposure

(i) Natural sources

Exposure to external radiation accounts for about 40% of the average worldwide natural radiation dose, the rest being due to internal exposure, mainly from ^{222}Rn (Table 1.1).

Most of the natural exposure to X- and γ-rays is from terrestrial sources, and depends on the concentration of (natural) radioactive materials in the soil and building materials. Cosmic rays contribute substantially to the effective dose and are practically the only natural source of neutron exposure. Cosmic ray dose at sea level is mainly from muons, electrons, and photons with about 8% of the effective dose from neutron interactions. The neutron fraction increases to a peak of about 40% at a height of around 4000 m. The cosmic ray dose increases with altitude and also is greater at higher latitudes (UNSCEAR, 2000a).

UNSCEAR (2000a) gives detailed data for exposure in various regions of the world. Average outdoor external dose rates for different countries cover the range 18–93 nGy/h. The population-weighted average is 59 nGy/h (0.52 mSv per year). Areas of very high dose rates above ~10000 nGy/h have been reported from various sites throughout the world.

The population-weighted average effective dose of neutrons was estimated to be 100 μSv per year by UNSCEAR (2000a).

(ii) Medical uses

The medical uses of radiation include diagnostic examinations and therapy. Radiotherapy is intended to deliver high doses to target organs of the order of tens of Gy (UNSCEAR, 2000a). Assessing the risk to non-target organs may be important in some cases.

The dose per medical diagnostic examination is generally of the order of 0.1–20 mGy. While lower than doses from radiotherapy, diagnostic examinations are the main source of radiation from medical use. The use of X- and γ-rays for

medical purposes is distributed very unevenly throughout the world (Table 1.2). UNSCEAR (2000a) reported an increase in the overall frequency of diagnostic X-ray examinations but the frequency was static or had shown decreases in some countries (Fig. 1.4). The majority of the world population receives no exposure in a given year from X- and γ-irradiation in medical diagnosis, while the effective dose may be up to 100 mSv for a small number of people. Doses due to diagnostic X-rays are changing rapidly with time as technologies develop (NCRP, 2009).

The average levels of radiation exposure due to the medical uses of radiation has been increasing (Fig. 1.5; UNSCEAR, 2000a), in particular due to increasing use of computed tomography (CT), angiography, and interventional procedures in developed countries (Fig. 1.6). The estimated global annual effective dose from all diagnostic uses of radiation was estimated to be 1.2 mSv per person in 1991–96, compared to 1.0 mSv in 1985–90. In 2006, US citizens received a collective effective dose from medical procedures 7.3 times greater than was the case in the early 1980s (NCRP, 2009).

For the same examination, doses may vary by an order of magnitude, and reducing the highest doses can reduce collective dose without a reduction in diagnostic information (Watson *et al.*, 2005).

Conventional radiographs form the majority of radiographic examinations with doses from < 0.01 up to ~10 mSv per procedure (Watson *et al.*, 2005). The use of digital imaging techniques to replace film-screen combinations has become widespread in some countries (see e.g. Hart *et al.* (2005) for a detailed review of practices in the United Kingdom).

Doses to the breast from mammography examinations are of the order of 1.5 mGy with large variations depending on breast characteristics (Young & Burch, 2000; Schubauer-Berigan *et al.*, 2002). In Germany, 18% of first mammographies were on women less than 30 years old and 31% on women 30–39 years old (Klug *et al.*, 2005). In USA, 60% of women had their first mammography exams by the age of their 40th year, and in France 45.8% during the age of 45–50 years (Spyckerelle *et al.*, 2002; Colbert *et al.*, 2004).

Table 1.1 Average radiation dose from natural sources

Source	Worldwide average annual effective dose (mSv)	Typical range (mSv)
External exposure		
Cosmic rays	0.4	0.3–1.0[a]
Terrestrial γ-rays	0.5	0.3–0.6[b]
Internal exposure		
Inhalation (mainly radon)	1.2	0.2–10[c]
Ingestion	0.3	0.2–0.8[d]
Total	2.4	1–10

[a] Range from sea level to high-ground elevation
[b] Depending on radionuclide composition of soil and building materials
[c] Depending on indoor accumulation of radon gas
[d] Depending on radionuclide composition of foods and drinking-water
From UNSCEAR (2000a)

Computed tomography scanning has become widely available in many developed countries. The effective dose per examination is considerably higher than that from most conventional radiographic procedures, and its use is increasing (Brenner & Hall, 2007). Doses per procedure are in the range of 1.5 mSv to over 25 mSv (UNSCEAR, 2000a).

Fluoroscopy results in much higher doses than radiography. The doses may vary widely: modern equipment with image amplifiers results in lower doses than older equipment with fluorescent screens, but high doses may still be received. Advances in technology have facilitated the development of increasingly complex radiological procedures for angiography and interventional radiology, and effective doses per procedure from under 10 to over 80 mSv, depending on the complexity of the procedure, have been reported (UNSCEAR, 2000a).

Table 1.2 Radiation exposures from diagnostic medical examinations

Population per physician	Annual number of examinations per 1000 population	Average annual effective dose to population (mSv)
< 1000	920	1.2
1000–3000	150	0.14
3000–10000	20	0.02
> 10000	< 20	< 0.02
Worldwide average	**330**	**0.4**

From UNSCEAR (2000a)

The medical use of neutrons and protons in radiotherapy is limited at present.

(iii) General population

Estimates of the average doses received by the general population are reviewed regularly by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2000a), and by many national bodies, such as the Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit in Germany (BMU, 2007), the National Council on Radiation Protection and Measurements in the USA (NCRP, 2009), and the Radiation Protection Division of the Health Protection Agency in the United Kingdom (Watson *et al.*, 2005).

Fig. 1.7 shows in a) the distribution of average exposures to ionizing radiation in the United Kingdom (Watson *et al.*, 2005) and in b) and c) how the distribution in the USA has changed between the early 1980s and 2006 (NCRP, 2009). The distribution of some of the components in different countries may vary by an order of magnitude.

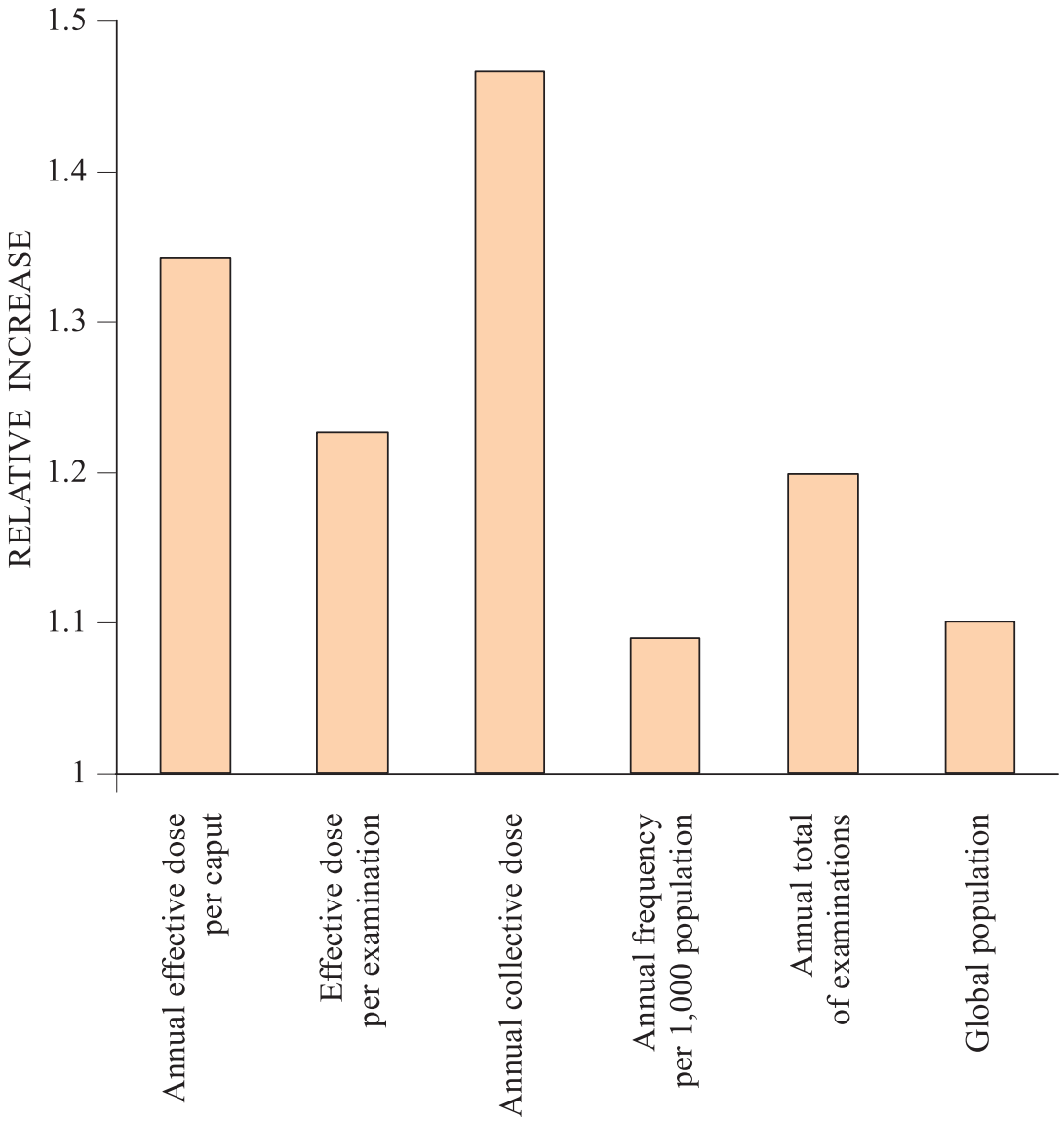
(iv) Nuclear explosions and production of nuclear weapons

The atomic bombings of Hiroshima and Nagasaki, Japan, in 1945 exposed hundreds of thousands of people to substantial doses of external radiation from γ-rays with a small fraction due to neutrons (~1%) and some internal exposure. For the survivors, the latest estimates of the doses using dosimetry system DS02 (Young & Kerr, 2005) are available for 113251 persons in the Life Span Study of whom 93741 were within 10 km of the hypocentres. Of these, 44464 had doses < 0.5 mGy and 35393 had doses > 10 mGy (Cullings *et al.*, 2006). The mean of known doses for survivors at about 1600 m was roughly 170 mGy (Preston *et al.*, 2004).

Atmospheric nuclear explosions were carried out, mostly in the northern hemisphere, between 1945 and 1980. The most intense period of testing was between 1952 and 1962. In all, approximately 543 atmospheric tests have been carried out, with a total yield of 440 Mt (megatonne) explosive power (UNSCEAR, 2000a). Since 1963, nuclear tests have been conducted mainly underground, and the principal source of worldwide exposure due to weapons testing is the earlier atmospheric tests. The global average committed effective dose (which includes the sum of all doses that will be received over a period of 50 years from internal irradiation) is 3.5 mSv, of which, 0.5 mSv is from external irradiation (UNSCEAR, 2000a). Annual average total radiation doses are currently ~8 μSv per year, of which, < 3 μSv per year is from external irradiation.

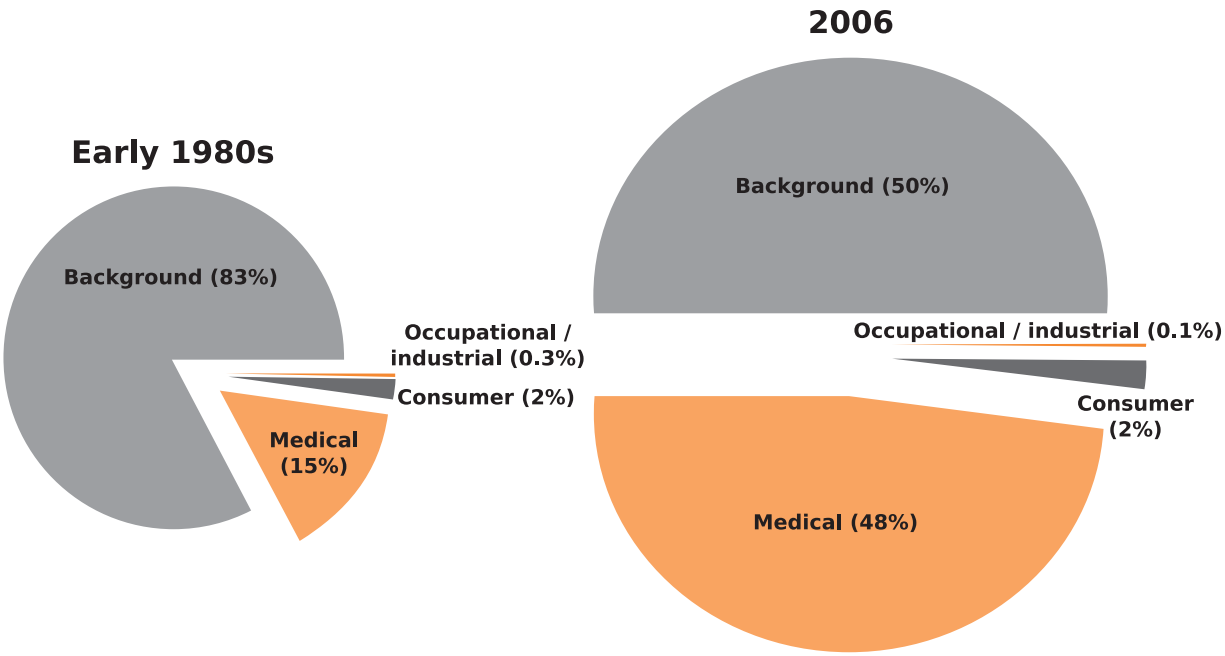
People living near the sites where nuclear weapons were tested received doses varying considerably in magnitude. Those near to the Nevada test site in the USA received an estimated average dose of about 3 mSv (Anspaugh *et al.*, 1990). After a US test in 1954 at Bikini atoll in the Marshall Islands, the residents of Rongelap and Utirik atolls (230 persons) received high external exposures (1900 mSv), mainly from short-lived radionuclides, with 67 persons receiving doses of 1750 mSv on Rongelap (Conard *et al.*, 1980). At Semipalatinsk in the former Soviet Union, atmospheric tests between 1949 and 1963, exposed 10000 people in settlements bordering the test site with doses ranging up to several Gy (Tsyb *et al.*, 1990).

Fig. 1.4 Temporal trends in global practice with medical X-ray examinations: average frequencies and doses for 1991–96 relative to previous estimates for 1985–90



Adapted from UNSCEAR (2000a)

Fig. 1.5 Comparison of distribution of collective dose values (S) or effective dose (Eus) for the categories of exposure as reported for the early 1980s and for 2006



	Early 1980s	2006
S: Collective effective dose (person-Sv)	835,000	1,870,000
E_{us} : Effective dose per individual in the US population (mSv)	3.6	6.2

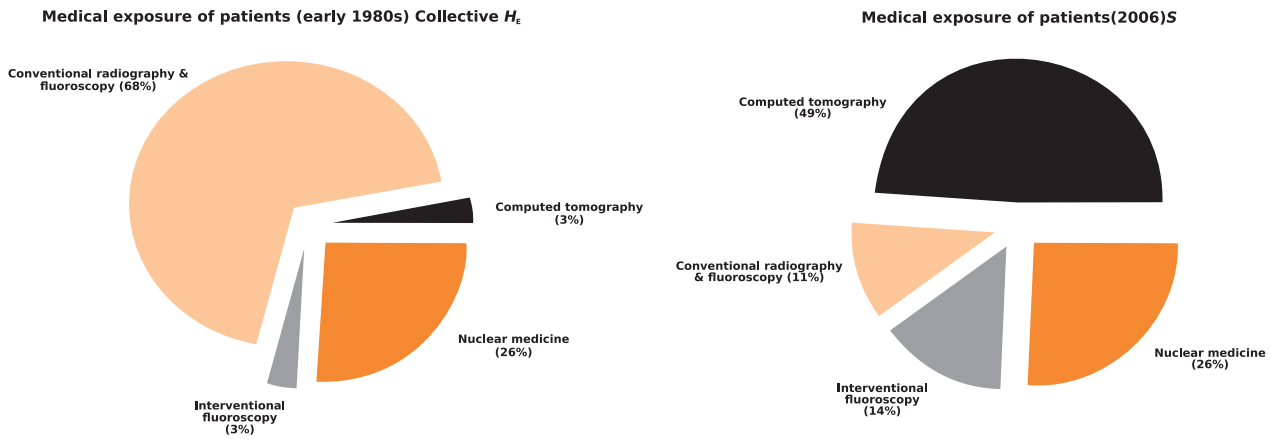
Adapted from NCRP (1987, 2009)

γ-ray exposures to the local population resulting from the production of weapons material and chemical separation can be considerable. For example, the release of nuclear wastes from the Mayak complex into the Techa River from a military plant of the former Soviet Union, resulted in organ doses up to 5.2 Gy at bone surfaces (median 0.37 Gy), mainly from internal radionuclides, with half of the much lower external doses lying between 0.0017 and 0.0062 Gy (Degteva *et al.*, 2006).

(v) Nuclear power production

Assuming that the generation of electrical energy by nuclear power reactors lasts for 100 years, the maximum collective dose for the entire fuel cycle (mining and milling, enrichment and fuel fabrication, reactor operation, fuel processing, waste disposal, transport of radioactive materials) has been estimated by UNSCEAR (2000a). If the present annual generation of 250 gigawatt continues for 100 years, the internal plus external dose to an individual of the general population would be less than 0.2 μSv per year. Evrard *et al.* reported an estimated dose of 0.17 μSv per year due to gaseous discharge in 2107 "communes" located in the vicinity of 23 French nuclear facilities, including all power plants (Evrard *et al.*, 2006). Most of the exposure is due to internal irradiation.

Fig. 1.6 Comparison of collective dose values for CT, conventional radiography and fluoroscopy, interventional fluoroscopy, and nuclear medicine (as % of total collective dose) as reported for the early 1980s (123700 person-Sv) (left: NCRP, 1989), and for 2006 (899000 person-Sv) (right: NCRP, 2009). For E_{US}, the same percentages apply. Collective dose quantities are S for 2006 and collective effective dose equivalent H_E for NCRP (1989).



	Early 1980s	2006
S: Collective effective dose (person-Sv)	123,700	899,000
E_{US}: Effective dose per individual in the U.S. population (mSv)	0.53	3.00

Adapted from NCRP (2009)

(vi) Accidents

For the Mayak, Windscale, and Chernobyl accidents, see Section 1.3.1 above.

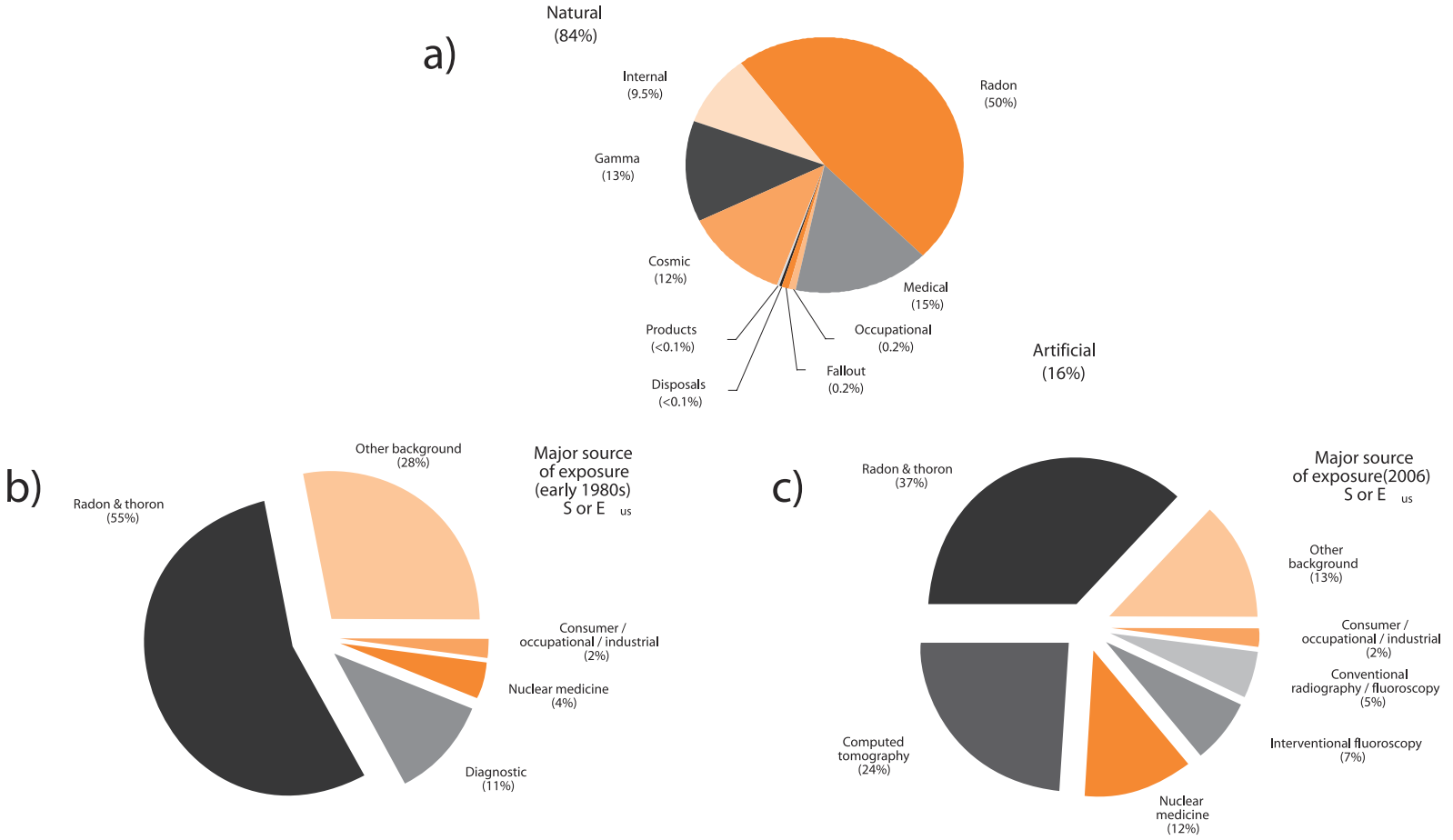
Sealed sources used for industrial and medical purposes have occasionally been lost, stolen or damaged, resulting in exposure of members of the public to these materials. Examples include the sale of a Cobalt-60 (^{60}Co) source as scrap metal in the city of Juarez, Mexico, in 1983 (Marshall, 1984); the theft and breaking up of a ^{137}Cs source in Goiânia, Brazil, in 1987 (IAEA, 1988); and the retrieval of a lost ^{60}Co source in Shanxi Province, the People's Republic of China, in 1992 (UNSCEAR, 1993). IAEA publications contain information on accidental irradiation during medical procedures, in particular Safety Report Series No. 17 (IAEA, 2000). While these incidents result in significant individual doses to a small number of people, the collective effective doses are not large. The steady increase in the use of sources of ionizing radiation has led to an increase in the number of fatalities, despite progress in radiation protection.

(vii) Occupational exposures

Occupational exposure to radiation occurs during nuclear power production and fuel recycling, military activities, industrial operations, flying and medical procedures (see above for details). Average annual effective doses are in Table 1.3 (UNSCEAR, 2000a). The average annual effective dose for occupational workers has reduced from 1.9 mSv in 1975–79 to 0.6 mSv in 1990–94.

Mean doses to medical radiation technologists in the US have reduced from 100 mSv per

Fig. 1.7 Percentage contribution of each natural and man-made radiation source



(a) UK population, average annual dose to the population = 2.7 mSv
(b) Distribution of S or E_{US} for the major sources of exposure for the early 1980s (NCRP, 1987). The percent values have been rounded to the nearest 1%. The total for S is 835,000 person-Sv and the total for E_{US} is 3.6 mSv, using a U.S. population of 230 million for 1980.
(c) Distribution of S or E_{US} for the major sources of exposure for 2006. The percent values have been rounded to the nearest 1 %. The total for S is 1,870,000 person-Sv and the total for E_{US} is 6.2 mSv, using a U.S. population of 300 million for 2006. The other background category consists of the external (space and terrestrial) and internal subcategories.
Adapted from Watson *et al.* (2005), NCRP (1987), NCRP (2009)

year before 1940 to 2.3 mSv per year during 1977–84 (Simon *et al.*, 2006). In recent years, worldwide annual doses have also been reduced from 0.6 mSv in 1980–84 to 0.33 mSv in 1990–94 (UNSCEAR, 1993, 2000a).

Occupational exposure to neutrons constitutes a small fraction of the total effective dose and occurs mainly in the nuclear industry. In a United Kingdom compilation of dose to nuclear workers (Carpenter *et al.*, 1994), the upper limit of the neutron component was estimated to be 3% of the total exposure. In the USA, more than 10000 nuclear workers per year receive measurable neutron doses (NCRP, 1987).

Neutron sources are used to chart progress in the search for gas and oil resources. For oil-well loggers, doses of 1–2 mSv per year were reported in one study (Fujimoto *et al.*, 1985), and in another (Inskip *et al.*, 1991), only seven of 1344 workers received above-threshold (0.02 mGy) doses.

The exposure of commercial aircraft crews to neutrons depends on the flight route and on the number of flight hours with secondary neutrons from galactic cosmic rays contributing about 10–15% of the dose at an altitude of 10 km. Watson *et al.* (2005) reviewed United Kingdom data by summarizing findings of Warner Jones *et al.* (2003) and Irvine & Flower (2005) and estimated overall average annual doses for all aircrew as 2 mSv from natural radiation and 19 μSv from the transport of radioactive material.

Staff involved in radiotherapy with neutrons are exposed mainly to γ- and β-rays due to activation of the room and equipment. The dose rates are well below 1 μGy/h and are not detectable by personal dosimetry (Smathers *et al.*, 1978; Finch & Bonnett, 1992; Howard & Yanch, 1995). Individuals are exposed to neutrons largely through the use of high-energy photon beams (> 15 MeV), which produce photo-neutrons (Hall *et al.*, 1995; Ongaro *et al.*, 2000), and also through the use of high-energy proton-therapy beams, which produce secondary neutrons (Brenner & Hall, 2008).

Table 1.3 Occupational radiation exposures

Source/practice	Number of monitored workers (thousands)	Average annual effective dose (mSv)
Man-made sources		
Nuclear fuel cycle (incl. uranium mining)	800	1.8
Industrial uses of radiation	700	0.5
Defence activities	420	0.2
Medical uses of radiation	2320	0.3
Education/veterinary	360	0.1
Enhanced natural sources		
Air travel (crew)	250	3.0
Mining (other than coal)	760	2.7
Coal mining	3910	0.7
Mineral processing	300	1.0
Above-ground workplaces (radon)	1250	4.8

Adapted from UNSCEAR (2000a)

The neutron energy spectrum to which individuals may be exposed varies widely, depending on the neutron source and the degree of moderation undergone by the neutrons. In most occupational settings, the neutron spectrum will be a degraded fission spectrum. For example, for workers occupationally exposed to low neutron doses from nuclear reactors or similar settings, the important neutron energy range in terms of dose deposition is, on average, from about 10–100 keV (Worgul *et al.*, 1996). Doses from radiotherapy-related photoneutrons are dominated by somewhat higher neutron energies (100–1000 keV) (Ongaro *et al.*, 2000), while the dose from secondary neutrons from galactic cosmic rays (De Angelis *et al.*, 2003), or from proton radiotherapy (Zheng *et al.*, 2007), will generally be dominated by higher-energy neutrons.

Astronauts are exposed to high doses of space radiation, which consists of protons, heavy ions

and secondary neutrons produced by galactic cosmic ray interactions, particularly if they go beyond low earth orbits. Based on data from a human phantom torso, the organ dose rates outside the International Space Station have been derived by Reitz *et al.* (2009) and are in the range of ~0.2–1.0 mGy/day. Data for average personnel badge doses for previous space missions give similar figures (Cucinotta *et al.*, 2008). The estimated dose (Cucinotta & Durante, 2006) for a lunar mission of 180 days is 60 mGy, and for a Mars exploration of 1000 days it is 420 mGy. The relative biological effectiveness for these heavy ions may be as high as 40.

1.3.2 α- and β-emitting radionuclides, internally deposited

(a) Tritium

(i) Nuclear weapons producion

Because the amount of ^{3}H needed for nuclear weapons purposes is relatively small, the facilities used to produce it tend to be much smaller than those used to produce plutonium, consequently the number of workers exposed to ^{3}H also tends to be small. The secrecy often associated with military ^{3}H production means that there are also relatively few ^{3}H worker cohorts identified from this activity. Relaxation of secrecy associated with military ^{3}H production in the United Kingdom in the last 10 years has meant that several hundred workers are now known to have potentially been exposed to ^{3}H at the Capenhurst and Chapelcross sites (HPA, 2007).

(ii) Nuclear power production

With heavy-water moderated reactors, such as the CANDU design, ^{3}H exposures normally account for the majority of the workers' dose.

(iii) Occupational exposure

^{3}H has also been used to produce self-illuminating devices (the β-particle emissions are used to stimulate light production in a suitable phosphorescent material) used in various applications including watches, gun sights, and signs. For example, about 100000 self-illuminating exit signs were produced per year in the USA during 1983–2002 (PSI, 2003), containing a total of approximately 100 PBq (petabecquerel, 10^{15} becquerel) of ^{3}H.

(b) Phosphorus-32

(i) Medical use

^{32}P, in the form $^{32}PO_4$, has been used in the treatment of *polycythaemia vera* since 1939. This has been the primary medical use for this radionuclide, representing ~5% of all therapeutic use of radionuclides in a survey of 17 European countries (Hoefnagel *et al.*, 1999) but only ~1% worldwide (UNSCEAR, 2000a). Individual treatments typically involve the use of 150–170 MBq of $^{32}PO_4$ (UNSCEAR, 2000a) administered orally or intravenously.

^{32}P has also been used as a radioactive tracer, for purposes such as identifying tumours as an aid in surgical removal. Historically, ^{32}P was also used in the treatment of leukaemia (both chronic myelocytic leukaemia and chronic lymphocytic leukaemia).

(c) Strontium-90

As exposure to ^{90}Sr is mostly in conjunction with other fission products, further information on exposures is given in the mixed fission products section below.

(d) Iodine-131

As exposure to ^{131}I can often be in conjunction with other fission products, further information on exposures is also given in the mixed fission products section below.

(i) Medical use

Radioiodine has been used in the treatment of hyperthyrodism and cancer of the thyroid for more than 50 years, and is by far the most common internal emitter used for therapeutic

purposes. It should also be noted that radioiodine treatment can be a source of external exposure to other people, and it is the main source of exposure to the public and relatives from patients who have received unsealed radionuclides (ICRP, 2004).

(ii) Accidents

Windscale fire

The Windscale fire in 1957, in the United Kingdom, resulted in the release of a total of 1.5×10^{15} Bq of radioisotopes. Because of the design of this reactor, which incorporated the filtration of exhausted coolant air, mainly gaseous and volatile radioisotopes escaped (^{133}Xe (14×10^{15} Bq), ^{210}Po (0.09×10^{15} Bq)) including 1.4×10^{15} Bq of ^{131}I. Prompt action to limit exposure to ^{131}I resulted in low doses being released to the general public; however, workers at the plant involved in efforts to extinguish the fire did receive larger than normal exposures (UNSCEAR, 1993; IARC, 2001).

Three Mile Island

Initially, the activity released during the Three Mile Island reactor accident in the USA was largely contained within the primary containment building but gaseous and volatile radionuclides including ^{133}Xe (370×10^{15} Bq) and ^{131}I (550×10^{9} Bq) were subsequently released into the environment (UNSCEAR 1993; IARC, 2001).

Chernobyl

Following the Chernobyl accident, reported individual thyroid doses ranged up to several tens of Gy, while average doses range from a few tens of mGy to several Gy (UNSCEAR, 2000b; Cardis *et al.*, 2006a, b).

(e) Caesium-137

As exposure to ^{137}Cs is mostly in conjunction with other fission products, further information on exposures is given in the mixed fission products section below.

(f) Radon

(i) Natural sources

Internal exposures from Naturally Occurring Radioactive Materials (NORM) are generally dominated by the isotopes in the ^{232}Th and ^{238}U decay chains, particularly ^{222}Rn and its progeny. ^{222}Rn makes by far the largest contribution to average individual internal exposures to the public from natural sources (see Table 1.1). ^{222}Rn concentration in buildings varies greatly, typically from less than 10 Bq/m^3 to more than 100 Bq/m^3 (UNSCEAR, 2006), depending on factors such as local geology and air movement (restricted ventilation in places such as caves can lead to much greater ^{222}Rn concentrations).

Residential ^{222}Rn concentrations can vary appreciably in different parts of the home, with basement ^{222}Rn concentrations typically 50% higher than on the ground floor (Field *et al.*, 2000, 2006). ^{222}Rn concentrations within homes in the same neighbourhood can also vary appreciably due to subtle aspects of building construction, such as cracks and fissures in the foundation, and ventilation of the home (Radford, 1985). Residential ^{222}Rn concentrations also exhibit seasonal variation, both within and between years (Pinel *et al.*, 1995; Krewski *et al.*, 2005). One other source of ^{222}Rn can be from domestic water supplies.

(ii) Occupational exposure

Because ^{222}Rn is formed from the radioactive decay of ^{238}U which is ubiquitous in the Earth's crust, high levels of ^{222}Rn gas have historically been found in underground mines (Committee on Health Risks of Exposure to Radon (BEIR VI, 1999)). Since the discovery of lung disease in underground miners exposed to high levels of ^{222}Rn in the 19th century, subsequently confirmed to be lung cancer in the 20th century, ^{222}Rn concentrations in mines were greatly reduced in the interest of industrial hygiene. Currently, ^{222}Rn concentrations in underground mines are

generally well below the current occupational exposure guideline of 2 working-level month/year (WLM/yr) in ventilated mines (1 WLM is exposure for 1 month (170 h) at 1 WL (working-level) corresponding to 130000 MeV of potential α energy released by the short-lived progeny in equilibrium with 100 pCi of ^{222}Rn in one litre of air (3.7 kBq/m^3)). Assuming a breathing rate of 1.2 m^3/h, the cumulative intake of 1 WLM is 0.755 MBq. Although historical exposures in underground mines have exceeded residential exposures by a factor up to a 1000-fold or more, this difference has been much reduced by a factor of 20–30-fold in recent years.

(g) Radium

(i) Occupational exposure

The practice of painting clock dials with radium-based paint to make them luminous was introduced just before the First World War. The production and application of luminous paint soon became an industry, particularly in the USA. Because of the precision required in applying these radium-based paints, 'Dial painters' or 'Luminisers' (as they were commonly known) frequently 'tipped' their brushes (i.e. brought the bristles to a point) using their mouths, and as a result would ingest some of the paint and the radium it contained. The use of radium-based paints has also occurred in Germany, the United Kingdom, and many other countries throughout the world (IARC, 2001).

(h) Thorium-232

(i) Medical use

Thorium dioxide (ThO_2) was first used as an X-ray contrast medium for splenography in the 1920s, and from 1931, a commercial preparation containing it, under the trade name 'Thorotrast', was marketed as a general vascular contrast medium. Thorotrast was administered by instillation or injection and was widely used throughout the world. It has been estimated that as many as 2.5 million individuals may have been exposed to it, before it was replaced by other contrast media in the 1950s (IARC, 2001).

(i) Uranium

(i) Natural source

Uranium is naturally present in small amounts almost everywhere in soil, rock including well water, and groundwater. Higher levels are present in natural uranium ores.

(ii) Occupational exposure

As it is the raw material for most nuclear power generation, uranium is ubiquitous in the nuclear fuel cycle: from mining and initial processing to enrichment and/or fuel manufacturing, power production, and reprocessing.

Exposure can involve natural, depleted and/or enriched uranium, in a wide variety of chemical forms (IARC, 2001).

(j) Plutonium

(i) Nuclear weapons production and testing

The USA was the first nation to pursue plutonium production as a means to construct a nuclear weapon, but the populations of exposed individuals tend to be compartmentalised and/or widely dispersed. The two largest continuous populations of workers exposed to plutonium are those at the Mayak Production Association in the southern urals, the Russian Federation, and those at the Sellafield (formerly Windscale) plant in the United Kingdom. Both of these facilities have plutonium worker cohorts of over 10000 individuals, with exposures starting in the late 1940s (Mayak) and early 1950s (Sellafield).

Political pressure to develop nuclear weapons as rapidly as possible both during and in the decade after the Second World War resulted in considerable internal exposure, primarily to plutonium. Unfortunately this tends to be the period in which monitoring data is most lacking, particularly for Mayak, where exposures were

the largest, with many individuals having no monitoring information at all.

(ii) Occupational exposure

The reprocessing of irradiated nuclear fuel, and to a lesser extent the production of mixed oxide 'MOX' fuel assemblies, can result in exposure to plutonium.

(k) Mixed fission products

Information on some major individual fission products (^{90}Sr, ^{131}I, ^{137}Cs) is given above. However, because of the stochastic nature of fission-product production, fission products are always produced in mixtures; and consequently, exposures are often to mixtures of fission products. Assessment of doses from mixed fission products that have been released into the environment are frequently dependent on environmental transport models.

(i) Southern urals

As stated previously, Mayak, the former Soviet Union's main production facility for weapons-grade plutonium was built near the town of Ozersk in the southern urals, the Russian Federation, in the 1940s. Operations at this facility resulted in several major, and persistent minor, releases of activity into the surrounding environment, particularly the Techa river and the surrounding area (IARC, 2001).

(ii) Techa river

During 1949–56, 100 PBq (100×10^{15} Bq) of activity were released into the Techa–Isset–Tobol river system. Of the approximately 28000 people living in settlements near the Techa river during this period, around 7500 were relocated during 1953–60 because of their exposure to radionuclides (UNSCEAR, 2000a).

(iii) Kyshtym accident

The Kyshtym accident released 74 PBq of radionuclides. The region contaminated by this accident had a population of approximately 273000 people and around 11000 of these had to be relocated, including 1500 that had previously been resettled from the Techa River area (UNSCEAR, 2000a).

(iv) Karachay lake

The Karachay lake accident released 0.022 PBq of radionuclides into the environment and distributed them over a wide area (UNSCEAR, 2000a).

(v) Chernobyl

The Chernobyl accident released substantial amounts of radionuclides into the environment including ^{131}I (1760 PBq) and ^{137}Cs (85 PBq), and these radionuclides were dispersed over an enormous area. The two main groups exposed were individuals working on recovery operations (so called liquidators) at the reactor site and members of the general population living in the vicinity of the site. A total of 116000 members of the public were evacuated from a 30-km area around the Chernobyl site following the accident, and 226000 recovery operators worked at the site or within this evacuated zone during the following year.

2. Cancer in Humans

X-radiation and γ-radiation were previously classified as Group 1 carcinogens by a previous *IARC Monograph* (IARC, 2000). This classification was based on increased risk of several cancers associated with X- and γ-rays, including leukaemia (excluding chronic lymphocytic leukaemia), breast cancer in women exposed before the menopause, cancer of the thyroid gland among people exposed during childhood, non-melanoma skin cancer, and cancer of the stomach, colon, and lung.

Epidemiological information on the carcinogenic effects of X- and γ-rays comes from studies of people exposed to radiation from the

detonations of atomic weapons, from medical procedures, and in occupational or environmental settings. The epidemiological findings that have been reported since the previous *IARC Monograph* (IARC, 2000) have been reviewed, with an emphasis on large, well designed studies with adequate assessment of radiation doses. Major reviews of the literature and risk estimates provided by UNSCEAR (UNSCEAR, 2008b) and the US National Academy of Sciences Council Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation (National Research Council, 2006) on radiation risks by cancer sites were also reviewed. The recent evidence is summarized by sources of exposure first, and then both earlier and more recent evidence is reviewed by cancer site. Cohort and case-control studies of cancer following X-ray exposure are summarized in Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.1.pdf and Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.2.pdf, and following γ-ray exposure in Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.3.pdf and Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.4.pdf.

2.1 Detonation of atomic bombs

The study of Japanese atomic bomb (A-bomb) survivors holds an important place in the literature on radiation epidemiology. Atomic bombs were dropped on Hiroshima and Nagasaki in August 1945. Survivors' external radiation doses were primarily from exposure to γ-radiation, although there was also a neutron contribution. Several years after the bombings, the Atomic Bomb Casualty Commission initiated a large population-based study of mortality and disease risk in relation to survivors' distance from the hypocentres of the atomic bombings (Francis *et al.*, 1955; Ishida & Beebe, 1959). That study, known as the Life Span Study (LSS), became the foundation for much of the ongoing research on mortality and cancer incidence among the Japanese A-bomb survivors (Shimizu *et al.*, 1990; Preston, *et al.*, 1994). The experiences of the Japanese A-bomb survivors have shown that the effect of exposure to detonation of atomic weapons persists for decades, and has an impact on the development of a wide range of malignant diseases.

The LSS provides an extremely important source of information about radiation health effects. The study cohort encompasses a large number of people, including men and women, exposed to a wide range of doses at all ages. An important development since of the previous *IARC Monograph* has been the introduction of revised radiation dose estimates for the A-bomb survivors: the Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagaski Dosimetry System 2002 (DS02) (Young & Kerr, 2005). Individual dose estimates for survivors within 2 km of the bombings are based on estimates of penetrating radiation emitted by the bombs and the location and shielding of survivors derived from interviews conducted in the late 1950s and early 1960s. Dose estimates for other survivors are based on less detailed information on shielding provided during interviews.

The LSS study does not provide information on the impact of radiation on cancer risk during the years immediately after the bombings. Follow-up for mortality started in 1950, and follow-up for cancer incidence in 1958. Furthermore, inclusion in the LSS cohort required people to have survived for at least 5 years after the bombings. Questions have been raised about potential biases associated with the impacts of early mortality on subsequent radiation risks, and about potential differences between survivors as a function of age at the time of the bombings and distance from the hypocentres (Cologne & Preston, 2000; Pierce *et al.*, 2007). Due to potential "healthy survivor effect," selection bias might be expected

to attenuate risk estimates or obscure evidence of associations rather than to induce spurious positive associations in the LSS; values for the magnitude of dose-related selective survival assumed in a recent study suggested a modest potential for bias in dose–response estimates (Pierce *et al.*, 2007). The DS02 system focuses on the prompt γ and neutron doses from the bomb detonations, but survivors could have also received doses from fallout and neutron activation of soil and other materials (Imanaka *et al.*, 2008; Tanaka *et al.*, 2008), which are not accounted for in current epidemiological analyses of the LSS data. Assumptions about the relative biological effectiveness of the neutron component of survivors' doses may have a substantial impact on quantitative estimates of γ-radiation dose effects (Walsh *et al.*, 2004).

Since the previous *IARC Monograph*, reports on the associations between the DS02-estimated dose and mortality due to leukaemia and solid cancers (Preston *et al.*, 2004) and solid cancer incidence (Preston *et al.*, 2007) have been published. The extension of follow-up of these cohorts, and the resultant increase in the number of cancer cases ascertained, has increased the ability to conduct site-specific analyses of cancer risks as well as permitted analyses that can characterize the risk of cancer in this population more than five decades after the bombings. Some recent analyses suggest a U-shaped pattern of association of the excess relative risk per Sievert (ERR/Sv) with age at exposure for solid cancers (Preston *et al.*, 2007; Little, 2009). Results of these analyses are discussed below along with results from a recent analysis examining cancer risks following in-utero exposure to radiation from the atomic bombings.

2.1.1 Leukaemia

Preston *et al.* (2004) analysed the association between leukaemia mortality during 1950–2000 and DS02 estimates of bone-marrow dose. There was clear evidence of excess risk of leukaemia among the A-bomb survivors, which increased with increasing magnitude of estimated dose, as illustrated by the ratio of the fitted excess to the expected background number of cases by category of dose (Table 2.5). The largest excess risks were observed for those exposed at younger ages, the excess tended to diminish in magnitude with time since exposure, and the exposure–response relationship appeared to be linear-quadratic. UNSCEAR (UNSCEAR, 2008b) and the US National Academy of Sciences Council Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation (National Research Council, 2006) have also reported analyses of leukaemia mortality in the LSS using the DS02 dose estimates and mortality data through 2000; both have shown the association between leukaemia mortality and the exposure.

Analyses of mortality by type of leukaemia among the Japanese A-bomb survivors during 1950–2000 have found that the ERR/Gy for acute myeloid leukaemia was best described by a quadratic dose–response function that peaked approximately 10 years after exposure. Mortality associated with acute lymphocytic leukaemia or chronic myeloid leukaemia was best described by a linear dose–response function that did not vary with time since exposure, while adult T-cell leukaemia was not associated with estimated bone-marrow dose (Richardson *et al.*, 2009).

No updates of analyses of leukaemia incidence in the LSS have been reported since the previous *IARC Monograph*.

2.1.2 Solid cancers

Preston *et al.* (2004) reported an analysis of all solid cancer mortality using DS02 dose estimates and mortality follow-up information for the period of 1950–2000. The ratio of the fitted excess to the expected background number of cases increased with dose (Table 2.6). The excess

Table 2.5 Association between leukaemia mortality during the period 1950–2000 and DS02 estimates of bone-marrow dose among A-bomb survivors in Japan

Weighted marrow dose category (Sv)	Subjects	Person–years	Leukaemia death	Expected background	Fitted excess
< 0.005	37407	1376521	92	84.9	0.1
0.005–0.1	30387	1125891	69	72.1	4.0
0.1–0.2	5841	208445	14	14.5	4.7
0.2–0.5	6304	231149	27	15.6	10.4
0.5–1	3963	144276	30	9.5	18.9
1–2	1972	71485	39	4.9	27.7
2+	737	26589	25	1.6	28.2
Total	**86955**	**3184256**	**296**	**203.0**	**93.0**

risk of solid cancer appeared to be linear in dose, with modifying effects of gender, age at exposure, and attained age.

Unlike recent analyses of mortality in the LSS, which included 86611 people, recent analyses of cancer incidence in the LSS also include the Hiroshima or Nagasaki residents who were temporarily not in either Hiroshima or Nagasaki or were more than 10 km from the hypocentre in either city at the time of the bombings. Preston *et al.* (2007) reported analyses of incidence data during 1958–98 from 105427 people who had DS02 dose estimates and who were alive, and had not been diagnosed with cancer as of 1958. The data for solid cancer incidence were consistent with a linear dose–response over a range of 0–2 Gy. Approximately 850 (about 11%) of the cases among cohort members with doses to the colon in excess of 0.005 Gy were estimated to be associated with A-bomb radiation exposure. Significant radiation-associated increases in incidence were reported for cancer of the oral cavity, oesophagus, stomach, colon, liver, lung, non-melanoma skin, breast, ovary, bladder, nervous system, and thyroid. Although there was no indication of a statistically significant dose–response for cancer of the pancreas, prostate, and kidney, the excess relative risks for these sites were also consistent with that for all solid cancers as a group. Elevated risks were seen for the five broadly classified histological groups considered, including squamous cell carcinoma, adenocarcinoma, other epithelial cancers, sarcomas, and other non-epithelial cancers. While the ERR/Gy was modelled with a linear term, the fit suggested departures at older ages, driven in part by the lung cancer risk.

Although the previous *IARC Monograph* noted that there was no association between radiation dose and thyroid cancer incidence among those over the age of 14 years when exposed, more recent analyses have shown positive associations between radiation dose and thyroid cancer incidence among adult female A-bomb survivors (ERR/Gy = 0.70; 95%CI: 0.20–1.46) (Richardson, 2009a). The ERR/Gy among men was −0.25 (90%CI: < 0–0.35). In that study, the number of thyroid cancer cases among women (n = 241) was nearly 5-fold the number of cases among men (n = 55).

Results for site-specific solid cancers in the LLS are discussed later in this section.

Table 2.6 Association between mortality from solid cancers during the period 1950–2000 and DS02 estimates of bone-marrow dose among A-bomb survivors in Japan

Weighted marrow dose category (Sv)	Subjects	Person–years	Solid cancer death	Expected background	Fitted excess
< 0.005	38507	1415830	4270	4282	2
0.005–0.1	29960	1105215	3387	3313	44
0.1–0.2	5949	218670	732	691	41
0.2–0.5	6380	232407	815	736	99
0.5–1	3426	125243	483	378	116
1–2	1764	64689	326	191	113
2+	625	22302	114	56	64
Total	**86611**	**3184356**	**10127**	**9647**	**479**

2.1.3 *Cancers after irradiation in utero, and pre-conception exposure*

Preston *et al.* (2008) reported on cancer incidence during the period 1958–2000 among A-bomb survivors exposed to radiation *in utero*. While prior work had focused on the excess risk of cancer in the first years of life following in-utero irradiation, Preston *et al.* found evidence of an association between in-utero irradiation and excess solid cancer risk in the period starting approximately 13 years after the atomic bombings in Japan. The optimal model indicated relationships between radiation dose in both in-utero and childhood exposures and risk of solid cancers, with modifications by a (negative) power of attained age. The ERR/Sv at age 50 years was 1.0 (95%CI: 0.2–2.3) for the in-utero cohort, slightly lower but not significantly different from the ERR in the early childhood-exposed cohort at this age (ERR/Sv, 1.7; 95%CI: 1.1–2.5). Excess absolute rates (EAR) at age 50 years increased markedly with attained age among those exposed in early childhood (EAR/10^4 person–year Sv, 56; 95%CI: 36–79) but exhibited little change in the in utero group (EAR/10^4 person–year Sv, 6.8; 95%CI: < 0–49) (Preston *et al.*, 2008).

There have been updated analyses of cancer incidence (Izumi *et al.*, 2003a) and cancer mortality (Izumi *et al.*, 2003b) with regard to pre-conception exposure in the F_1 cohort of the Japanese A-bomb survivors. The study participants were conceived between 1 month and 38 years after the atomic bombings, and one or both parents were in either the cities of Hiroshima or Nagasaki at the time of the bombing and for childbirth. During the 40-year period of follow-up, 575 solid cancer cases and 68 haemopoietic neoplasms were recorded, and no associations were found with either paternal or maternal pre-conception dose ($P > 0.1$) (Izumi *et al.*, 2003b). During the 1946–99 period of follow-up, 314 solid cancer deaths were recorded, and no associations were found with either paternal or maternal pre-conception dose ($P > 0.1$) (Izumi *et al.*, 2003a).

2.2 Fallout from nuclear weapons testing

2.2.1 *Semipalatinsk*

Several hundred nuclear weapons tests, including above-ground tests, occurred at Semipalatinsk, Kazakhstan, then part of the former Soviet Union. Nearby residents were exposed to external doses of γ-radiation and internal doses due to the inhalation and ingestion of radioactive fallout from these nuclear

weapons tests (including ^{131}I, ^{137}Cs, and ^{90}Sr). Estimating dose for these residents has shown to be difficult, and there are conflicting estimates of the magnitude of the doses received by individuals living in villages in the vicinity of Semipalatinsk (Simon *et al.*, 2003). The study was comprised of two groups: 9850 permanent inhabitants of rural areas of the Semipalatinsk region and 9604 permanent inhabitants of villages located several hundred kilometres east of the test site. For the first group, individual internal and external doses were available, and a collective estimate of 20 mSv due to fallout from multiple atmospheric nuclear testing was used for the second group. Risk estimates were found to differ depending on whether they were based on the total cohort (including the comparison villages) or on the exposed villages only. The estimate of the ERR/Sv for all solid tumours was 1.77 (95%CI: 1.35–2.27) based on the data for the total cohort. A significant trend with dose was observed for cancer of the stomach (ERR/Sv, 1.68; 95%CI: 0.83–2.99), lung (ERR/Sv, 2.60; 95%CI: 1.38–4.63), and of the female breast (ERR/Sv, 1.28; 95%CI: 0.27–3.28). However, selection bias regarding the comparison group could not be ruled out. Based on the data for the exposed group only, the estimate of the ERR/Sv for all solid tumours was 0.81 (95%CI: 0.46–1.33); for cancer of the stomach, 0.95 (95%CI: 0.17–3.49); lung, 1.76 (95%CI: 0.48–8.83), and of the female breast, 1.09 (95%CI:–0.05–15.8) (Bauer *et al.*, 2005).

2.3 Medical exposures

The previous *IARC Monograph* (IARC, 2000) reviewed several studies of second cancer risk following X- or γ-radiation therapy for a first cancer. Since then, several reports have been published on second cancers following radiotherapy; in these studies patients were treated primarily, or solely, with X-rays. However, studies of cancers following radiation therapy pose several challenges: (i) the doses may be so high that cell-killing (the objective of the treatment) overwhelms cancer initiation, (ii) radiotherapy is often coupled with chemotherapy and their separate impacts may be difficult to distinguish, and (iii) patients with existing cancers may differ from the general population (raising questions about making generalisations of radiation risk estimates derived from studies of cancer survivors). In this *Monograph*, the risk of the second cancer following radiation therapy reported by recent X-ray studies is reviewed.

2.3.1 Cancer of the lung

The only major X-ray study with good quality radiation dosimetry and follow-up is an international Hodgkin disease study (Gilbert *et al.*, 2003). This resulted in an ERR/Gy of 0.15 (95%CI: 0.06–0.39) after adjusting for chemotherapy and smoking. As with all studies considered, a potential problem with this study is ascertainment and adjustment for cigarette smoking. Although the methods used in this study are thorough, they are based on data abstracted from medical records, in which assessment of smoking before the primary cancer was mainly retrospective, so recall bias cannot be excluded. This study demonstrated that the interaction of radiation and chemotherapy risk was consistent with an additive relationship on the logistic scale, and a multiplicative relationship could be rejected ($P = 0.017$). Conversely, the interaction of radiation and smoking was consistent with a multiplicative relationship, but not with an additive relationship ($P < 0.001$). There was little indication of modification of ERR by age at exposure, years since exposure (after a 5-year minimum latent period) or attained age (Gilbert *et al.*, 2003).

2.3.2 Cancer of the female breast

The major X-ray studies with good quality radiation dosimetry and follow-up are nested case–control studies in an international Hodgkin disease study (Travis *et al.*, 2003) and the Netherlands Hodgkin disease study (van Leeuwen *et al.*, 2003), as well as the French-United Kingdom childhood cancer (Guibout *et al.*, 2005) and the US scoliosis (Ronckers *et al.*, 2008) cohorts. The excess risk in the first three of these studies are reasonably consistent, at least for those women not treated with chemotherapy: the ERR/Gy was 0.15 (95%CI: 0.04–0.73) in Travis *et al.* (2003), 0.06 (95%CI: 0.01–0.13) in van Leeuwen *et al.* (2003), and 0.13 (95%CI: < 0.0–0.75) in Guibout *et al.* (2005). A higher point estimate of risk (ERR/Gy, 2.86; 95%CI: −0.07–8.62) was observed in the US scoliosis study (Ronckers *et al.*, 2008), but in view of the wide confidence interval this can be considered as consistent with the other three studies. A complication in some of these radiotherapy studies is radiation dose to the ovaries; the analyses of van Leeuwen *et al.* (2003) and Travis *et al.* (2003) suggested that women receiving large ovarian doses (> 5 Gy) were at lower risk of radiation-induced breast cancer, presumably because of ovarian ablation and induced menopause.

Ronckers *et al.* (2008) reported a significantly greater dose–response ($P = 0.03$) for women who reported a family history of breast cancer in first- or second-degree relatives (ERR/Gy, 8.37; 95%CI: 1.50–28.16) compared with those without affected relatives (ERR/Gy, −0.16; 95%CI: < 0–4.41). Susceptibility alleles of single genes that confer a high risk of breast cancer are rare in the general population, but some studies have shown modification of breast cancer risk by family history (Easton, 1999). Recent genome-wide association studies (GWAS) have established several new breast cancer susceptibility loci (Pharoah *et al.*, 2008). The study of Millikan *et al.* (2005) suggests that other common polymorphisms in DNA-repair genes may modify the effects of low-dose radiation exposure from medical sources. They reported a stronger trend of breast cancer risk with the number of diagnostic X-rays among women with 2–4 variant codons in *XRCC3*, *NBS1*, *XRCC2*, *BRCA2* genes than in women with only 0 or 1 variant codons in those genes. [The Working Group noted, however, that the results were inconclusive, being based only on self-reported exposure to ionizing radiation from medical sources, which may therefore be subject to recall bias. The particular genes used, and the gene "dose" cut-off points (≥ 2 versus < 2 codons), both presumably chosen *a posteriori*, may imply uncertainties regarding the statistical significance in this study].

2.3.3 Cancer of the brain/central nervous system

The major X-ray studies with good quality radiation dosimetry and follow-up are the Israeli tinea capitis study and the International Childhood Cancer Study. The ERR/Gy in the first of these, a cohort study of survivors of tinea capitis (a fungal infection of the scalp) treated with radiation in childhood, was 4.63 (95%CI: 2.43–9.12) for benign meningioma and 1.98 (95%CI: 0.73–4.69) for malignant brain tumour (Sadetzki *et al.*, 2005). In the second study (Neglia *et al.*, 2006), the ERR/Gy was 0.33 (95%CI: 0.07–1.71) for gliomas, 1.06 (95%CI: 0.21–8.15) for meningiomas, and 0.69 (95%CI: 0.25–2.23) for all central nervous system tumours. Therefore, in both studies, there is a pattern of increased relative risk per unit dose for benign brain tumours compared with malignant brain tumours, a pattern also observed in some other earlier studies (Little *et al.*, 1998).

2.3.4 Leukaemia

Modern classifications of leukaemia and other lymphatic and haematopoietic malignancies (e.g. Swerdlow *et al.*, 2008) are based on cytogenetic and

molecular principles that do not always coincide with the International Classification of Diseases. There are generally considered to be three main radiogenic subtypes: acute lymphocytic leukaemia, which is a leukaemia of precursor cells of either B-cell or T-cell origin; acute myeloid leukaemia, whose lineage and subtype are generally defined according to the French-American-British (FAB) system (Bennett *et al.*, 1982; Harris *et al.*, 1999); and chronic myeloid leukaemia, whose predominant haematological feature is an elevated white-cell count in the peripheral blood, and which is characterized cytogenetically by the Philadelphia chromosome (Linet & Cartwright, 1996).

The major X-ray studies with good quality radiation dosimetry and follow-up are an international nested case–control study on testicular cancer survivors and the New York tinea capitis cohort. The ERR at 10 Gy in the first of these (Travis *et al.*, 2000) was 3.27 (95%CI: 1.2–13). In the New York tinea capitis study (Shore *et al.*, 2003), the standardized incidence ratio (SIR) for leukaemia (following an average dose of about 4 Gy to cranial marrow) was 3.2 (95%CI: 1.5–6.1). No dose–response analysis was reported [possibly as a consequence of the small number of cases (eight leukaemias, of which six were non-chronic lymphocytic leukaemia in the exposed group versus one chronic lymphocytic leukaemia in the control group)].

For the risk of leukaemia associated with prenatal exposures, see Section 2.1.3 and Section 2.6.19.

2.4 Occupational studies

2.4.1 IARC 15-country study

IARC conducted a collaborative study of cancer risk among workers in the nuclear industry. Analyses include 407391 nuclear industry workers who were individually monitored for external irradiation (primarily γ-rays), and were employed in the industry for at least 1 year (Cardis *et al.*, 2007). Workers with potential for substantial doses from other radiation types and workers with potential for high-dose-rate exposure were excluded from the main study population. [The Working Group noted that strengths of the study include a common core study protocol and quantitative radiation dose estimates based upon personal dosimetry. Although it was a large study, the 15-country study's statistical power was limited by small numbers of workers with higher doses. As is common in occupational cohort mortality studies, there was limited information available on confounders, such as cigarette smoking.] Concerns about confounding by smoking were addressed indirectly by the examination of associations between radiation dose and non-malignant respiratory disease. Smoking-related and non-smoking-related solid cancers were also analysed separately. No statistically significant association was seen between radiation dose and any of the groups of non-malignant respiratory diseases examined. Risk estimates for mortality from all non-malignant respiratory disease and for chronic bronchitis and emphysema combined were positive but not significantly different from zero, and risk estimates for chronic pulmonary disease not otherwise specified and for emphysema were negative, but not significantly different from zero.

Among the cancer categories examined, a significant positive dose–response association was reported for lung cancer mortality; no other specific cancer category exhibited a statistically significant dose–response trend. The ERR/Sv was 1.86 (90%CI: 0.49–3.63) for cancer of the lung, 1.93 (90%CI: < 0–7.14) for leukaemia (excluding chronic lymphocytic leukaemia), 0.97 (90%CI: 0.27–1.80) for all cancers excluding leukaemia, 0.59 (90%CI:–0.16–1.51) for all cancers excluding leukaemia, lung and pleura, and 0.87 (90%CI: 0.16–1.71) for all solid cancers (Cardis *et al.*, 2007). Risk estimates for all

cancers excluding leukaemia and for all cancers excluding leukaemia, lung and pleural cancers were very similar and above 200 mSv. [The Working Group noted that, therefore, although confounding by smoking might be present, it is unlikely to explain all of the increased risk for all cancers excluding leukaemia in that study.] Results by country show that, for all cancers excluding leukaemia, the ERR/Sv estimate for Canadian workers (6.65; 90%CI: 2.56–13.0) was larger than for workers from most other countries with sizable numbers of deaths, statistically significant, and exerted a substantial influence on the overall pooled analysis.

The ERR/Sv was greater for those exposed at ages over 50 years than for those exposed at younger ages. With regard to all cancers excluding leukaemia, ERR/Sv by age at exposure was 1.74 (90%CI: 0.24–3.58) for age > 50 years, 1.32 (90%CI: 0.12–2.71) for age 35–50 years, and –1.07 (90%CI: < 0–1.24) for age < 35 years. The respective values were 3.87 (90%CI: 0.92–7.93), 1.52 (90%CI:–0.71–4.36) and 2.51 (90%CI:–1.96–8.89) for cancer of the lung, and 5.01 (90%CI: < 0–14.7), –1.59 (90%CI: < 0–3.02) and 1.51 (90%CI: < 0–11.6) for leukaemia excluding chronic lymphocytic leukaemia.

An analysis examined the association between radiation dose and chronic lymphocytic leukaemia mortality among 295963 workers in the seven countries with chronic lymphocytic leukaemia deaths; there were 65 chronic lymphocytic leukaemia deaths in this cohort (Vrijheid *et al.*, 2008). The relative risk (RR) at an occupational dose of 100 mSv compared to 0 mSv was 0.84 (95%CI: 0.39–1.48) under the assumption of a 10-year exposure lag. [The Working Group noted that this study had little power due to low doses (average cumulative bone marrow dose, 15 mSv), short follow-up periods, and uncertainties in chronic lymphocytic leukaemia ascertainment from death certificates.]

2.4.2 United Kingdom radiation workers

Although many workers included in the United Kingdom National Registry for Radiation Workers (NRRW) were included in the IARC 15-country study, Muirhead *et al.* (2009) reported on an updated and expanded study of mortality and cancer incidence through December 2001 among 174541 people occupationally exposed to ionizing radiation, based on the NRRW. Doses from the internal deposition of radionuclides were not generally available and were not used in the analysis, nor was individual information available on smoking history. The analyses focused on doses from penetrating radiation at the surface of the body, estimated using personal dosimeters. Mortality and cancer incidence were studied in relation to dose after adjusting – through stratification – for age, gender, calendar period, industrial classification (industrial/non-industrial/unknown), and first employer. Within each stratum, the number of deaths or cases expected in each category for cumulative external dose (0–, 10–, 20–, 50–, 100–, 200–, 400+ mSv) was calculated, conditional on the total overall dose categories, and presuming no effect of dose. There was a highly significant negative association observed between mortality from bronchitis, emphysema and chronic obstructive disease and dose (ERR/Sv, –1.04; 90%CI: –1.35, –0.59) [The Working Group noted that this would be consistent with lower smoking prevalence among workers who accrued higher radiation doses and suggests potential negative confounding in analyses of radiation dose–response associations for smoking-related cancers]. There was a positive association between radiation dose and mortality due to leukaemia excluding chronic lymphocytic leukaemia (ERR/Sv, 1.71; 90%CI: 0.06–4.29), and also between radiation dose and mortality due to all malignant neoplasms excluding leukaemia (ERR/Sv, 0.28; 90%CI: 0.02–0.56). In analyses of cancer incidence, positive associations were also seen with leukaemia

excluding chronic lymphocytic leukaemia (ERR/Sv, 1.78; 90%CI: 0.17–4.36), and all malignant neoplasms excluding leukaemia (ERR/Sv, 0.27; 90%CI: 0.04–0.51). Among the leukaemia subtypes, the strongest evidence of association, from both analyses of mortality and incidence data, was for chronic myeloid leukaemia; there was no evidence of an association between chronic lymphocytic leukaemia (mortality or incidence) and radiation.

2.4.3 US radiation workers

The results of several epidemiological studies of US radiation workers have been reported, providing results that extend those encompassed by the US workers included in the 15-country study. An analysis of leukaemia mortality among workers employed at the Savannah River site, a large cohort of US nuclear weapons workers that is independent of the 15-country study, reported a positive association between leukaemia mortality and radiation dose under a 3-year lag assumption (ERR/Sv, 4; 90%CI: –0–12). The association was of larger magnitude for leukaemia excluding chronic lymphocytic leukaemia (ERR/Sv, 8; 90%CI: 1–20) and for myeloid leukaemia (ERR/Sv, 12; 90%CI: 2–35), and these associations tended to diminish in magnitude with time since exposure to radiation (Richardson & Wing, 2007). A positive association was also observed between lymphoma mortality and radiation dose under a 5- and 10-year lag (ERR/Sv, 6.99; 90%CI: 0.96–18.39 and ERR/Sv, 8.18; 90%CI: 1.44–21.16, respectively; Richardson *et al.*, 2009). A nested case–control study of leukaemia among workers at four US nuclear weapons facilities and the Portsmouth naval shipyard reported a positive [but highly imprecise] association between leukaemia mortality and radiation dose (ERR/Sv, 1.44; 90%CI: <–1.03–7.59; Schubauer-Berigan *et al.*, 2007). A case–control study of lung cancer among workers at Portsmouth Naval shipyard reported some evidence of a positive association with lung cancer, which was substantially attenuated after adjusting for medical X-ray exposures (Yiin *et al.*, 2007). Matanoski *et al.* (2008) reported the results of analyses of leukaemia, lymphohaematopoietic cancers, lung cancer, and mesothelioma among workers from shipyards involved in nuclear powered ship overhauls. The study included 28000 workers with cumulative doses of 5 mSv or more, 10462 workers with cumulative doses less than 5 mSv, and 33353 non-nuclear workers. Exposures were almost exclusively due to γ-radiation. There was evidence of dose-related increases in leukaemia, lung cancer, and lymphohaematopoietic cancers. In an internal comparison of workers with 50.0 mSv exposures to workers with exposures of 5.0–9.9 mSv, the relative risk was 2.41 (95%CI: 0.5–23.8) for leukaemia, 1.26 (95%CI: 0.9–1.9) for lung cancer, and 2.94 (95%CI: 1.0–12.0) for lymphohaematopoietic cancers.

2.4.4 Mayak

Since the previous *IARC Monograph* (IARC, 2000), updated reports have been published on cancer risk among workers at the Mayak nuclear complex in the Russian Federation, another large cohort of nuclear workers not included in the IARC study. Exposures at Mayak included external γ-radiation exposure as well as internal α-particle exposure. A large number of workers, particularly those employed in the radiochemical and plutonium production facilities, had significant potential for plutonium exposures. Gilbert *et al.* (2004) investigated lung cancer mortality over the period 1955–2000 in a cohort of 21790 Mayak workers. The average cumulative external radiation dose among those monitored for radiation was 0.8 Gy. For external doses, the ERR/Gy was 0.17 (95%CI: 0.052–0.32) among men and 0.32 (95%CI: < 0–1.3) among women. [The Working Group noted that uncertainties in plutonium exposure assessment could lead to inadequate adjustment for the effects of internal exposures.]

Analyses restricted to Mayak workers who were monitored for plutonium or worked only in the reactor or auxiliary plants led to smaller estimates of ERR/Gy of external dose (ERR/Gy, 0.065; 95%CI: < 0–0.25) than obtained via the analysis of the full cohort (ERR/Gy, 0.10; 95%CI: < 0–0.29). The potential confounding by smoking was investigated in a subset of the cohort, and in that subcohort there was sparse data with which to evaluate the effects of external dose but the ERR/Gy was smaller when adjusted for smoking status (ERR/Gy, 0.027; 95%CI: < 0–0.18; Gilbert *et al.*, 2004). Shilnikova *et al.* (2003) reported that solid cancer and leukaemia death rates increased significantly with increasing γ-ray dose. For external doses, the ERR/Sv (adjusted for plutonium exposure) was 0.15 (90%CI: 0.09–0.20) for solid tumours and 0.99 (90%CI: 0.45–2.12) for leukaemia excluding chronic lymphocytic leukaemia.

2.4.5 Chernobyl clean-up workers

Kesminiene *et al.* (2008) reported the results of a case–control study of leukaemia and lymphoma incidence among Chernobyl liquidators from Belarus, the Russian Federation, and Baltic countries. The main analyses included 70 cases (40 leukaemia, 20 non-Hodgkin lymphoma, and ten other types) and 287 age-matched controls. Bone-marrow doses were estimated by the "RADRUE" (realistic analytical dose reconstruction with uncertainty estimation) individual reconstruction methods (Kryuchkov *et al.*, 2009). The overall ERR/Gy was 6.0 (90%CI: −0.2, 23.5; Kesminiene *et al.*, 2008). The dose–response relationship was of larger magnitude for non-Hodgkin lymphoma (ERR/Gy, 28.1; 90%CI: 0.9–243.0) than for leukaemia (ERR/Gy, 4.8; 90%CI: < 0, 33.1), although the confidence intervals were wide for both outcomes. The ERR/Gy for leukaemia excluding chronic lymphocytic leukaemia was 5.0 (90%CI: −0.38, 5.7) based on 19 cases and 83 controls; the risk estimate for chronic lymphocytic leukaemia (ERR/Gy, 4.7; 90%CI: −∞, 76.1) was similar to the estimate for all leukaemia combined (ERR/Gy, 4.8; 90%CI: −∞, 33.1).

Romanenko *et al.* (2008) reported results from a nested case–control study of leukaemia in a cohort of clean-up workers identified from the Chernobyl State Registry of Ukraine. The study included 71 cases of leukaemia diagnosed during 1986–2000, and 501 age- and residence-matched controls; bone-marrow doses were estimated by the RADRUE reconstruction method. The ERR/Gy of total leukaemia was 3.44 (95%CI: 0.47–9.78). Overall, the dose–response relationship for both chronic (ERR/Gy, 4.09; 95%CI: < 0–14.41) and non-chronic lymphocytic leukaemia (ERR/Gy, 2.73; 95%CI: < 0–13.50) was comparable.

While leukaemia and lymphoma incidence among Chernobyl liquidators from the Russian Federation were examined in the study by Kesminiene *et al.* (2008), analyses of mortality and cancer incidence among Russian liquidators were also reported by Ivanov (2007). In 1991–98, the ERR/Gy of death from malignant neoplasm was 2.11 (95%CI: 1.31–2.92). In 1991–2001, the ERR estimation for incident solid cancers was positive [but imprecise] (ERR/Gy, 0.34; 95%CI: −0.39–1.22; Ivanov, 2007).

2.5 Environmental studies

2.5.1 Techa River

Studies of environmental exposures to γ-radiation also provide insights into the carcinogenic effects of protracted exposures. A notable investigation of the effects of environmental exposures to γ-radiation concerns releases of radioactive materials into the Techa River in the southern urals, the Russian Federation, as a result of operations at the Mayak production facility. External exposures were primarily due to γ-radiation from contamination of the river shoreline and floodplains; in addition, internal

exposures resulted from the consumption of food and drink contaminated with radionuclides. Fission products were the largest component of the internal dose, and residents thus received internal γ-and β-radiation exposures. The ratio of external/internal radiation varied according to the site.

Since the previous *IARC Monograph*, several reports have been published on associations between radiation exposure and cancer among residents of villages along the Techa river. Krestinina *et al.* (2007) reported results on solid cancer incidence in a cohort of 17433 people who resided in villages along the Techa river, with follow-up from 1956–2002, in relation to the estimated cumulative stomach dose (approximately half from internal dose). There was a highly significant linear dose–response relationship between cumulative stomach dose and incidence of solid tumours (P = 0.004). Ostroumova *et al.* (2008) reported results on breast cancer incidence in a cohort of 9908 women with follow-up from 1956–2004. A significant dose–response relationship (P = 0.01) was reported between cumulative stomach dose and breast cancer incidence, with an estimated ERR/Gy of 5.00 (95%CI: 0.80–12.76). Ostroumova *et al.* (2006) reported results from a nested case–control study of leukaemia among residents near the Techa river. The study included 83 cases ascertained over a 47-year period of follow-up and 415 controls; in analyses of leukaemia excluding chronic lymphocytic leukaemia, the odds ratio at 1 Gy, estimated via a log-linear model, was 4.6 (95%CI: 1.7–12.3), 7.2 (95%CI: 1.7–30.0), and 5.4 (95%CI: 1.1–27.2) for total, external and internal red bone-marrow doses, respectively.

2.5.2 High-background radiation areas

Hwang *et al.* (2008) reported results on cancer risks in a cohort of Chinese residents in Taiwan, China, who received protracted low-dose-rate γ-radiation exposures from ^{60}Co-contaminated reinforcing steel used to build their apartments. The study included 117 cancer cases diagnosed during 1983–2005 among 6242 people with an average excess cumulative exposure estimate of about 48 mGy. There was a significant association between the estimated radiation dose and leukaemia excluding chronic lymphocytic leukaemia (hazard ratio (HR)/100 mGy, 1.19; 90%CI: 1.01–1.31); the HR/100 mGy estimated for breast cancer was 1.12 (90%CI: 0.99–1.21).

Nair *et al.* (2009) reported results on cancer incidence in Kerala, India, in an area known for high-background radiation from thorium-containing monazite sand. Cancer incidence in a cohort of 69958 residents aged 30–84 years was ascertained through to 2005 (average duration of follow-up, 10.5 years); the cumulative radiation dose for each individual was estimated based on outdoor and indoor dosimetry of each household. The median outdoor radiation levels were approximately 4 mGy per year; median indoor radiation levels were somewhat lower. The analysis, which included 1379 cancer cases and 30 leukaemia cases, found no cancer site was significantly related to cumulative radiation dose. The estimated ERR/Gy of cancer excluding leukaemia was −0.13 (95%CI: −0.58–0.46).

2.6 Synthesis

The previous *IARC Monograph* (IARC, 2000) states there is strong evidence for causal associations between X- and γ-radiation and several cancer sites, including those listed in Table 2.7. In this current *Monograph*, the Working Group re-evaluated the evidence (the earlier evidence and that published after the previous *IARC Monograph*) for those cancer sites, and similarly, found strong evidence of causation. The major publications on which the above conclusion is based are also listed in Table 2.7. The United States National Research Council (2006) and UNSCEAR (2008b) have also made similar conclusions for the cancer sites listed in Table 2.7.

Table 2.7 Cancer sites and tumours judged to have sufficient evidence for a causal association with X-ray and γ-ray exposure

Organ site	Selected key studies
Stomach	Boice *et al.* (1988), Mattsson *et al.* (1997), Carr *et al.* (2002), Preston *et al.* (2003, 2007)
Colon	Darby *et al.* (1994), Preston *et al.* (2003, 2007)
Lung	Weiss *et al.* (1994), Carr *et al.* (2002), Gilbert *et al.* (2003), Preston *et al.* (2003, 2007)
Basal cell skin carcinoma	Schneider *et al.* (1985), Ron *et al.* (1991, 1998), Little *et al.* (1997), Shore *et al.* (2002), Preston *et al.* (2007)
Female breast	Howe & McLaughlin (1996), Preston *et al.* (2002, 2003, 2007)
Thyroid	Lundell *et al.* (1994), Lindberg *et al.* (1995), Ron *et al.* (1995), Preston *et al.* (2007)
Leukaemia excluding chronic lymphocytic	Little *et al.* (1999), Travis *et al.* (2000), Preston *et al.* (2003, 2004), Muirhead *et al.* (2009)

The evidence for the other individual cancer sites is shown in Table 2.8. The focus has been on relatively large studies of good design, where good quality dosimetry has been carried out, and where the magnitude of the doses is generally substantial. Wherever possible, risk estimates from several studies were provided including the latest LSS incidence analysis (Preston *et al.*, 2007) and in some cases the latest LSS mortality data (Preston *et al.*, 2003), the International Radiation Study of Cervical Cancer Patients (IRSCCP; Boice *et al.* 1988), the United Kingdom ankylosing spondylitis data (Weiss *et al.*, 1994), the United Kingdom metropathia haemorrhagica study (Darby *et al.*, 1994), the NRRW (Muirhead *et al.*, 2009), and the IARC 15-country study (Cardis *et al.*, 2007). For certain cancer sites, some of these studies are largely uninformative (e.g. only standardized mortality ratios (SMRs) are given for various cancer sites in the metropathia haemorrhagica study), which were therefore omitted from Table 2.8.

2.6.1 Cancer of the salivary gland

This is a rare cancer site and has not been much studied in most of the major radiation-exposed cohorts (e.g. Boice *et al.*, 1988; Weiss *et al.*, 1994; Cardis *et al.*, 2007, Muirhead *et al.*, 2009). Nevertheless, there is a statistically significant positive dose–response relationship in the Japanese A-bomb survivor incidence data (Land *et al.*, 1996), and in the study of patients who received radiation therapy during childhood for benign conditions in the head and neck area (Schneider *et al.*, 1998). The estimated ERR/Sv for the incidence data of the Japanese A-bomb survivors was 4.47 (90%CI: 2.45–8.46) for malignant tumours, based on 31 cases, and for benign tumours the risk estimate was 1.71 (90%CI: 1.13–2.71), based on 64 cases (Land *et al.*, 1996). The ERR/Gy in the Schneider *et al.* (1998) study was −0.06 (95%CI: −∞–4.0) for malignant tumours, based on 22 cases, and 19.6 (95%CI: 0.16–∞) for benign tumours, based on 66 cases. Although data on dose–response are lacking, there are also indications of significant excess risk in the Israeli tinea capitis study (Modan *et al.*, 1998), and in the Rochester thymus irradiation study (Hildreth *et al.*, 1985; Table 2.8). In the Israeli study as in the LSS, risks for malignant tumours (RR, 4.49; 95%CI: 1.45–13.9) were greater than benign tumours (RR, 2.62; 95%CI: 1.10–6.25), in contrast to the pattern in the study of Schneider *et al.* (1998). In the Rochester study, there were eight benign tumours (RR, 4.4; 95%CI: 1.2–16.7), but no malignant tumour in the irradiated group. A non-significant excess risk (RR, 1.8; 95%CI: 0.4–8.9) for salivary gland tumours (two

malignant and four benign) was reported in the New York tinea capitis study (Shore *et al.*, 2003).

Preston *et al.* (2007) did not analyse this tumour in the most recent analysis of cancer incidence among the Japanese A-bomb survivors. [The Working Group analysed the publicly available data set using a linear relative risk model in which the expected number of cases in stratum i and dose group d is assumed to be given by $PY_{id}\lambda_d$ [1 + αD_{id}] fitted by Poisson maximum likelihood, and profile-likelihood-bounds derived (McCullagh & Nelder, 1989) using EPICURE (Preston *et al.*, 1998).

Here, PY_{id} is the number of (migration-adjusted) person–years of follow-up, λ_d is the (semi-parametric) background hazard rate (estimated separately for each stratum), and D_{id} is the DS02 organ dose in Sv (brain dose is used as a surrogate), using the neutron quality factor of 10 recommended by the ICRP (1991). The estimate of the ERR coefficient α is given in Table 2.8, and is seen to be statistically significant (2.42 per Sv; 95%CI: 0.48–6.70).]

In summary, although this is a rare cancer site, there are strong and highly statistically significant trends in the LSS data (Land *et al.*, 1996; Preston *et al.*, 2007), and trends of similar magnitude in the study of Schneider *et al.* (1998). There are indications of excess risk in several other radiotherapeutically exposed groups.

2.6.2 Cancer of the oesophagus

Cancer incidence data from the latest LSS data show a significant excess risk of oesophageal cancer (Preston *et al.*, 2007), as do the latest site-specific mortality data (Preston *et al.*, 2003), as reported in Table 2.8. The estimate of the ERR/Sv coefficient for the incidence data is 0.52 (90%CI: 0.15–1.0), based on 352 cases. For the LSS mortality data the ERR/Sv was broadly similar with 0.61 (90%CI: 0.15–1.2) for men, based on 224 deaths; and, 1.7 (90%CI: 0.46–3.8) for women, based on 67 deaths. There was also a statistically significant excess risk reported in the United Kingdom ankylosing spondylitis study (Weiss *et al.*, 1994); the ERR/Gy was 0.17 (95%CI: 0.09–0.25), based on 74 deaths.

In summary, there are strong and highly statistically significant trends in the LSS incidence and mortality data (Preston *et al.*, 2003, 2007), as is the case in the United Kingdom ankylosing spondylitis data (Weiss *et al.*, 1994). There are (statistically non-significant) indications of excess in several other studies (e.g. Boice *et al.* 1985; Muirhead *et al.* 2009; Table 2.8).

2.6.3 Cancer of the small intestine, including the duodenum

This is a rare cancer site and has not been much studied in most of the major radiation-exposed cohorts (e.g. Weiss *et al.*, 1994; Cardis *et al.*, 2007; Muirhead *et al.*, 2009). There was no significant excess risk and no evidence of a positive dose–response in the IRSCCP (Boice *et al.*, 1988): the odds ratio was 1.0 (90%CI: 0.3–2.9), based on 22 cases, despite the very high doses received (estimated to be several hundred Gy on average). Preston *et al.* (2007) did not analyse this tumour among A-bomb survivors. [The Working Group analysed the publicly available LSS incidence data set using a linear relative risk model (*Formula* 1) and obtained an ERR, given in Table 2.8, which is not statistically significant (ERR/Sv, 0.65; 95%CI: −0.32–4.89), based on 16 cases.]

In summary, for this rare cancer, there are essentially only two informative studies, the LSS incidence data (Preston *et al.*, 2007) and the IRSCCP (Boice *et al.*, 1988), but neither of which reports a statistically significant excess risk.

2.6.4 Cancer of the rectum

Among the survivors of the atomic bombings, mortality from cancer of the rectum was not clearly associated with radiation dose

Table 2.8 Summary of evidence for organ sites initially deemed to be potentially having limited evidence of carcinogenicity or inadequate evidence of carcinogenicity

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Salivary gland	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Land *et al.* (1996)	All malignant: 4.47 (2.45–8.46)[a]	Incidence	31	
					All benign: 1.71 (1.13–2.71)[a]	Incidence	64	
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	All malignant: 2.42 (0.48–6.70)	Incidence	34	Stratified linear RR model fitted to publicly available data, using brain dose
	Benign head & neck RT in childhood	200 KeV X-rays to head and neck	0.01–15.8 (4.2)	Schneider *et al.* (1998)	All malignant: −0.06 (−∞–4.0)	Incidence	22	
					All benign: 19.6 (0.16–+∞)	Incidence	66	
	Thymic enlargement	Thymus 250 kVp X-rays	Breast dose 0.01–19.51 (0.69)	Hildreth *et al.* (1985)	All malignant: RR, 0.0 (0.0–34.6)	Incidence	11	Women only
					All benign: RR, 4.4 (1.2–16.7)		1	
	New York tinea capitis	X-rays to scalp	(0.39 per treatment)	Shore *et al.* (2003), Harley *et al.* (1976)	RR, 1.8 (0.4–13)	Incidence	8	6 exposed, 2 unexposed cases
	Israeli tinea capitis: malignant	X-rays to scalp	0.63–2.86 (0.78) per treatment	Modan *et al.* (1998)	Malignant: RR, 4.49 (1.45–13.9)	Incidence	16	12 exposed, 4 controls
					Benign: RR, 2.62 (1.10–6.25)		22	14 exposed, 8 controls

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/ Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Oesophagus	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	0.52 (0.15–1.0)[a]	Incidence	352	80% of cases confirmed histologically
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	Men: 0.61 (0.15–1.2)[a] Women: 1.7 (0.46–3.8)[a]	Mortality	224 67	
	Ankylosing spondylitis	X-rays to spinal	90% range 0.48–10.16 (5.55)	Weiss *et al.* (1994)	0.17 (0.09–0.25)	Mortality	74	
	Metropathia haemorrhagica	X-rays to ovaries	90% range 0.02–0.11 (0.05)	Darby *et al.* (1994)	SMR, 0.97 (0.44–1.84)	Mortality	9	
	International Radiation Study of Cervical Cancer Patients	Mostly 200–400 kVp X-ray +radium +gamma to cervix	(0.35)	Boice *et al.* (1985)	0.26 (–1.1–1.3)[b]	Incidence	12	10-year survivors following the primary cancer
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	–1.6 (–4.3–1.5)[a d]	Mortality	144	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	0.15 (–0.84–1.72) 0.15 (–0.91–2.06)	Mortality Incidence	341 300	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Small intestine	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	0.65 (−0.32–4.89)	Incidence	16	Stratified linear RR model fitted to publicly available data, using colon dose
Cervical cancer		Mostly 200–400 kVp X-ray +radium +gamma to cervix	10–20	Boice *et al.* (1988)	OR, 1.0 (0.3–2.9)[a]	Incidence	22	RR trend not computed because of small number of non-exposed cases
Rectum	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 Sv (0.1)	Preston *et al.* (2007)	0.19 (−0.04–0.47)[a]	Incidence	838	90% of cases confirmed histologically
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	Men: −0.25 (< −0.3–0.15)[a] Women: 0.75 (0.16–1.6)[a]	Mortality	172 198	
	Ankylosing spondylitis	X-rays to spine	90% range 0.53–10.20 (4.12)[c]	Weiss *et al.* (1994)	0.03 (−0.03–0.10)[c]	Mortality	62	
	Metropathia haemorrhagica	X-rays to ovaries	90% range 3.4–6.3 (4.9)	Darby *et al.* (1994)	0.04 (−0.09–0.16)	Mortality	14	
	International Radiation Study of Cervical Cancer Patients	Mostly 200–400 kVp X-ray +radium +gamma to cervix	30–60	Boice *et al.* (1988)	0.02 (0.00–0.04)[a]	Incidence	488	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Rectum (contd.)	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	1.27 (< 0–7.62)[a]	Mortality	185	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	1.69 (–0.02–4.73) 1.31 (0.04–3.2)	Mortality Incidence	303 586	
Liver	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	0.30 (0.11–0.55)[a, e]	Incidence	1494	41% of cases histologically confirmed
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	Men: 0.39 (0.11–0.68)[a] Females: 0.35 (0.07, 0.72)[a]	Mortality Mortality	722 514	
	Ankylosing spondylitis	X-rays to spine	90% range 0.31–3.83 (2.13)	Weiss *et al.* (1994)	RR, 0.81 (0.40–1.44)	Mortality	11	Dose–response not calculated
	Metropathia haemorrhagica	X-rays to ovaries	90% range 0.12–0.55 (0.27)	Darby *et al.* (1994)	SMR, 0.33 (0.04, 1.21)	Mortality	2	Dose–response not calculated
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	6.47 (< 0–27.0)[a]	Mortality	62	
	United Kingdom NRRW primary liver	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	–1.50 (< –1.93–8.56) –0.65 (< –1.93–7.73)	Mortality Incidence	40 56	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/ Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Pancreas	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	0.26 (< −0.07–0.68)[a]	Incidence	512	52% of cases confirmed histologically
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	Men: −0.11 (< −0.3–0.44)[a] Females: −0.01 (−0.28-0.45)[a]	Mortality	163 244	
	Peptic ulcer	250 kVp X-ray	0.9–> 16 (13.5)	Carr *et al.* (2002)	Irradiated + not: 0.04 (0.00–0.08) Irradiated only: −0.03 (−0.10–0.05)	Mortality	59	
	Skin haemangioma	Radium-226 applicators	< 0.01–> 1.0 (0.09)	Lundell & Holm (1995)	25.1 (5.5–57.7)	Incidence	9	
	Ankylosing spondylitis	X-rays to spine	90% range 0.53–8.24 (4.52)	Weiss *et al.* (1994)	0.12 (0.05–0.20)	Mortality	84	
	Metropathia haemorrhagica	X-rays to ovaries	90% range 0.12–0.61 (0.29)	Darby *et al.* (1994)	SMR, 0.66 (0.30–1.26)	Mortality	9	Dose–response not calculated
	International Radiation Study of Cervical Cancer Patients	Cervix	0–> 3 (1.9)	Boice *et al.* (1988)	0.00 (−0.28–0.62) [a]	Incidence	221	
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	2.10 (−0.59–6.77)[a]	Mortality	272	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	−0.05 (−1.11–2.07) 0.08 (−1.07–2.51)	Mortality Incidence	330 320	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Bone & connective tissue	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	Bone: 1.01 (< 0–4.38) Connective tissue: 1.76 (< 0–6.41) Bone+connective tissue: 1.34 (0.14–3.74)	Incidence	18 23 41	Stratified linear RR model fitted to publicly available data, using skeletal dose
	Retinoblastoma patients		(0.0)	Wong *et al.* (1997)	0.19 (0.14–0.32)[b]	Incidence	81	
	Childhood radiotherapy (international)		(27)	Tucker *et al.* (1987)	0.06 (0.01–0.2)[a b]	Incidence	54	
	United Kingdom childhood cancer: bone		0–> 50 (10)	Hawkins *et al.* (1996)	0.16 (0.07–0.37)[b]	Incidence	49	
	Ankylosing spondylitis	X-rays to spine	90% range 1.42–7.82 (4.54)	Weiss *et al.* (1994)	Bone: RR, 3.29 (1.58–5.92) Connective tissue: RR, 2.83 (1.41–4.95)	Mortality	9 10	Dose–response not calculated
	Metropathia haemorrhagica: bone	X-rays to ovaries	90% range 1.0–1.6 (1.3)[g]	Darby *et al.* (1994)	SMR, 0.00 (0.00–4.01)	Mortality	0	Dose–response not calculated
	International Radiation Study of Cervical Cancer Patients: bone	Cervix	0–> 30 (22.0)	Boice *et al.* (1988)	RR, 1.34 (0.3–5.6)[a]	Incidence	15	RR trend not computed because of small number of non-exposed cases

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/ Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Bone & connective tissue (contd.)	International Radiation Study of Cervical Cancer Patients: connective tissue	Cervix	0–> 20 (7.0)	Boice *et al.* (1988)	−0.05 (−0.11–0.13)[a]	Incidence	46	
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	Bone: −8.4 (−10.0–17.2)[a d]	Mortality	16	
					Connective tissue: 0.32 (< 0–11.5)[a]		39	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	Bone: < −1.93 (< −1.93–28.51)	Mortality	8	
					Bone: 1.18 (< −1.93–52.16)	Incidence	17	
					Connective tissue: < −1.93 (< −1.93–7.49)	Mortality	31	
					Connective tissue: < −1.93 (< −1.93–1.42)	Incidence	58	
Skin cancers other than basal cell skin cancer								
Squamous cell carcinoma	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Ron *et al.* (1998)	< −0.1 (< −0.1–0.10)[a]	Incidence	69	
	New York tinea capitis	X-rays to scalp	3.3–6 scalp dose (4.75)	Shore *et al.* (2002)	Irradiated 7 cases vs unirradiated 0 cases	Incidence	7	
	Israeli tinea capitis	X-rays to scalp	5.5–24.4 scalp dose (6.8)	Ron *et al.* (1991)	Irradiated 0 cases vs unirradiated 2 cases	Incidence	2	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Melanoma	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Thompson *et al.* (1994)	0.22 (< 0–4.14)	Incidence	13	Stratified linear RR model fitted to publicly available data, using skeletal dose
	France-United Kingdom childhood cancer	Treatment at various sites	0–51 (3.1)	Guérin *et al.* (2003)	0.07 (0.00–0.15)	Incidence	16	
	IARC 15-country nuclear workers (bone)	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	0.15 (< 0–5.44)[a]	Mortality	87	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	1.39 (–0.65–5.6)	Incidence	261	
Uterus	A-bomb: uterine corpus	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	Uterine corpus: 0.29 (–0.14–0.95)[a] Uterine cervix + NOS: 0.06 (–0.14–0.31)[a] Uterine corpus, uterine NOS+cervix: 0.10 (–0.09–0.33)[a]	Incidence	184 978 1162	97% of cases confirmed histologically Cervix: 97% of cases confirmed histologically Uterine NOS: 55% of cases confirmed histologically

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/ Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Uterus (contd.)	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	0.17 (–0.10–0.52)[a]	Mortality	518	
	Ankylosing spondylitis	X-rays to spine	90% range 0.14–10.35 (4.94)	Weiss *et al.* (1994)	Uterus including cervix: ERR/Gy 0.09 (–0.02–0.19) Uterus apart from cervix: RR, 1.91 (0.92–3.51)	Mortality	10	
					Cervix: RR, 0.36 (0.07–1.04)		3	
	Metropathia haemorrhagica: uterine corpus +cervix	X-rays to ovaries	90% range 4.3–6.4 (5.2)	Darby *et al.* (1994)	0.09 (–0.02–0.19)	Mortality	25	
	International Radiation Study of Cervical Cancer Patients: uterine corpus	Mostly 200–400 kVp X-ray +radium +gamma to cervix	(165)	Boice *et al.* (1988)	OR, 1.34 (0.8–2.3)[a h]	Incidence	313	RR trend not computed because of small number of non-exposed cases
	IARC 15-country nuclear workers: uterus apart from cervix:	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	Uterus apart from cervix 0.16 (< 0–94.1)[a i]	Mortality	13	
					Cervix –0.11 (< 0, 131)[a]		14	
	United Kingdom NRRW: uterine corpus +cervix	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	17.81 (< –1.93–91.96) 10.52 (–0.50–48.02)	Mortality Incidence	19 58	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Ovary	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	0.61 (0.00–1.5)[a]	Incidence	245	88% of cases confirmed histologically
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	0.94 (0.07–2.0)[a]	Mortality	136	
	Ankylosing spondylitis	X-rays to spine	90% range 0.12–12.28 (5.53)	Weiss *et al.* (1994)	RR, 0.97 (0.52–1.67)	Mortality	13	
	Metropathia haemorrhagica	X-rays to ovaries	< 4.8–> 6.0 (5.3)	Darby *et al.* (1994)	0.02 (–0.08–0.12)	Mortality	18	
	International Radiation Study of Cervical Cancer Patients	Mostly 200–400 kVp X-ray +radium +gamma to cervix	0–> 50 (32.1)	Boice *et al.* (1988)	0.01 (–0.02–0.14)[a]	Incidence	309	
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	–9.1 (–10.0–15.8)[a d]	Mortality	35	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	< –1.93 (< –1.93–121.76)	Mortality	18	
					< –1.93 (< –1.93–88.75)	Incidence	15	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/ Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Prostate	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	0.11 (−0.10–0.54)[a]	Incidence	387	88% of cases confirmed histologically
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	0.21 (< −0.3–0.96)[a]	Mortality	104	
	Ankylosing spondylitis	X-rays to spine	90% range 0.18–0.71 (0.36)[j]	Weiss *et al.* (1994)	0.14 (0.02–0.28)	Mortality	88	
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	0.77 (< 0–4.58)[a]	Mortality	301	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	0.42 (−0.42–1.64) −0.18 (−0.73–0.57)	Mortality Incidence	702 1516	
Bladder	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	1.23 (0.59–2.1)[a e]	Incidence	469	88% of cases confirmed histologically
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	Men: 1.1 (0.2–2.5)[a] Women: 1.2 (0.10–3.1)[a]	Mortality	83 67	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Bladder (contd.)	Ankylosing spondylitis	X-rays to spine	90% range 0.20–4.85 (2.18)	Weiss *et al.* (1994)	0.24 (0.09–0.41)	Mortality	71	
	Metropathia haemorrhagica	X-rays to ovaries	90% range 4.3–6.4 (5.2)	Darby *et al.* (1994)	0.40 (0.15–0.66) SMR, 3.01 (1.84–4.64)	Mortality	20	
	International Radiation Study of Cervical Cancer Patients	Mostly 200–400 kVp X-ray +radium +gamma to cervix	30–60 Gy	Boice *et al.* (1988)	0.07 (0.02–0.17)[a]	Incidence	273	
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	–2.2 (–5.0–1.0)[a d]	Mortality	145	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	0.40 (–0.78–2.48) 0.65 (–0.28–1.96)	Mortality Incidence	301 748	
Kidney	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	0.13 (–0.25–0.75)[a] EAR, 0.25×10^{-4}/PY/Sv (0.07–0.53)[a]	Incidence	167	82% of cases confirmed histologically
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	Men: –0.02 (< –0.3–1.1)[a] Women: 0.97 (< –0.3–3.8)[a]	Mortality	36 31	
	Ankylosing spondylitis	X-rays to spine	90% range 0.71–11.74 (6.08)	Weiss *et al.* (1994)	0.10 (0.02–0.20)	Mortality	35	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/ Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Kidney (contd.)	Metropathia haemorrhagica	X-rays to ovaries	90% range 0.17–0.79 (0.40)	Darby *et al.* (1994)	SMR, 1.19 (0.39–2.78)	Mortality	5	Dose–response not calculated
	International Radiation Study of Cervical Cancer Patients	Mostly 200–400 kVp X-ray +radium +gamma to cervix	0–> 3 (2.0)	Boice *et al.* (1988)	0.71 (0.03–2.24)[a]	Incidence	148	
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	2.26 (< 0–14.9)[a]	Mortality	127	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	−1.03 (−1.57–0.39) −0.41 (−1.32–1.48)	Mortality Incidence	187 296	
Brain & CNS	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2007)	All brain & CNS: 0.62 (0.21–1.2)[a] Glioma: 0.56 (−0.2–2.0) Meningioma: 0.64 (−0.01–1.8) Schwannoma: 4.50 (1.9–9.2)	Incidence	281 56 110 64	81% of cases confirmed histologically
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (2003)	Men: 5.3 (1.4–16)[a] Women: 0.51 (< −0.3–3.9)[a]	Mortality	14 17	
	New York tinea capitis	Scalp irradiation	0.75–1.7 (1.4)	Shore *et al.* (2003)	1.1 (0.1–2.8) RR (treated:control), +∞ (1.2–+ ∞)	Incidence	7	SIR for brain cancer, 3.0 (1.3–5.9). No brain cancers were observed in the control group

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Brain & CNS (contd.)	Israeli tinea capitis	X-rays to scalp	1.0–6.0 (1.5)	Sadetzki *et al.* (2005)	All malignant: 1.98 (0.73–4.69) All benign: 4.63 (2.43–9.12)	Incidence	44 81	
	France-United Kingdom childhood cancer	Exposure of various sites	0–82.7 (6.2)	Little *et al.* (1998)	All malignant: 0.07 (< 0–0.62) All benign: > 1000 (0.25–> 1 000)	Incidence	12 10	
	Ankylosing spondylitis (spinal cord)	X-rays to spine	Brain 90% range 0.03–0.40 (0.20)	Weiss *et al.* (1994)	Spinal cord death 3.33 (0.08–18.6)	Mortality	1	
	Metropathia haemorrhagica	X-rays to ovaries	90% range 0.001–0.004 (0.002)	Darby *et al.* (1994)	SMR, 1.84 (0.84–3.49)	Mortality	9	Dose–response not calculated
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	–1.8 (–4.7–1.7)[a d]	Mortality	235	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	–1.36 (–1.85–0.55) –0.88 (–1.56–0.69)	Mortality Incidence	278 337	
Non-Hodgkin lymphoma	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Richardson *et al.* (2009)	1.12 (0.26–2.51)[a]	Mortality	84	Men, aged 15–64 yr at exposure
	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 Sv (0.1)	Preston *et al.* (1994)	Combined ERR/Sv, 0.05 (< 0–0.70) Men EAR, 0.56×10^{-4}/PY/Sv (0.08–1.39) Women EAR, 0×10^{-4}/PY/Sv (< 0–0.28)	Incidence	170	Stratified linear RR model fitted to publicly available data, using bone-marrow dose

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/ Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Non-Hodgkin lymphoma (contd.)	Ankylosing spondylitis	X-rays to spine	90% range 1.65–8.41 (5.10)[k]	Weiss *et al.* (1994)	RR, 1.74 (1.23–2.36)	Mortality	37	Dose–response not calculated because there was no clear appropriate organ dose
	Metropathia haemorrhagica	X-rays to ovaries	90% range 1.0–1.6 (1.3) [g]	Darby *et al.* (1994)	SMR, 0.75 (0.20–1.93)	Mortality	4	Dose–response not calculated
	Benign gynaecological disease	Exposure of pelvic area	(1.19)	Inskip *et al.* (1993)	RR (exposed:not), 0.9 (0.6–1.6)[a]	Mortality	53	Dose–response not calculated
	International Radiation Study of Cervical Cancer Patients	Mostly 200–400 kVp X-ray +radium +gamma to cervix	0–> 12 (7.1)	Boice *et al.* (1988)	OR, 2.51 (0.8–7.6)[a]	Incidence	94	RR trend not computed because of small number of non-exposed cases
	Savannah river site workers	Uniform whole body	0–> 0.3 Sv	Richardson *et al.* (2009)	7.62 (0.93–20.77)[a]	Mortality	51	
	Chernobyl liquidator study	Work in aftermath of Chernobyl accident	0–> 0.5 (0.013)	Kesminiene *et al.* (2008)	28.1 (0.9–243)[a]	Incidence	20	
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	0.44 (< 0–4.78)[a]	Mortality	248	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	0.78 (–0.66–3.4) 1.28 (–0.38–4.06)	Mortality Incidence	237 305	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Hodgkin disease	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (1994)	0.48 (< 0–3.96)	Incidence	21	Stratified linear RR model fitted to publicly available data, using bone-marrow dose
	Ankylosing spondylitis	X-rays to spine	90% range 1.65–8.41 (5.10)[k]	Weiss *et al.* (1994)	RR, 1.65 (0.88–2.81)	Mortality	13	Dose–response not calculated
	Metropathia haemorrhagica	X-rays to ovaries	90% range 1.0–1.6 (1.3)[g]	Darby *et al.* (1994)	SMR, 3.30 (0.90–8.46)	Mortality	4	Dose–response not calculated
	Benign gynaecological disease	Exposure of pelvic area	(1.19)	Inskip *et al.* (1993)	RR (exposed:not), 0.9 (0.3–3.2)[a]	Mortality	13	Dose–response not calculated
	International Radiation Study of Cervical Cancer Patients	Mostly 200–400 kVp X-ray +radium +gamma to cervix	0–> 12 (8.2)	Boice *et al.* (1988)	OR, 0.63 (0.2–2.6)[a]	Incidence	14	RR trend not computed because of small number of non-exposed cases
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	−0.18 (< −0.18–7.25)[a]	Mortality	44	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	< −1.93 (< −1.93–32.73) < −1.93 (< −1.93–12.55)	Mortality Incidence	33 67	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Multiple myeloma	A-bomb	Uniform whole body, mostly high-energy (2–5 MeV) gamma + small amount of high-energy neutrons	0–4 (0.1)	Preston *et al.* (1994)	EAR, 0.08×10^{-4}/PY/Sv (< 0–0.3)	Incidence	59	
	Ankylosing spondylitis	X-rays to spine	90% range 1.65–8.41 (5.10)[k]	Weiss *et al.* (1994)	RR, 1.62 (1.07–2.46)	Mortality	22	Dose–response not calculated because there was no clear appropriate organ dose
	Metropathia haemorrhagica	X-rays to ovaries	90% range 1.0–1.6 (1.3)[g]	Darby *et al.* (1994)	SMR, 2.59 (1.19–4.92)	Mortality	9	Dose–response not calculated
	Benign gynaecological disease	Exposure of pelvic area	(1.19)	Inskip *et al.* (1993)	RR (exposed:not), 0.6 (0.3–1.4)[a]	Mortality	21	Dose–response not calculated
	International Radiation Study of Cervical Cancer Patients	Mostly 200–400 kVp X-ray +radium +gamma to cervix	0–> 12 (7.1)	Boice *et al.* (1988)	RR, 0.26 (0.0–2.6)[a]	Incidence	49	RR trend not computed because of small number of non-exposed cases
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	6.15 (< 0–20.6)[a]	Mortality	83	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	1.20 (–1.08–7.31) 3.60 (0.43–10.37)	Mortality Incidence	113 149	

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Chronic lymphocytic leukaemia	Ankylosing spondylitis	X-rays to spine	0–> 7.00 (4.38)	Weiss *et al.* (1995)	RR, 1.44 (0.62–2.79)	Mortality	7	Dose–response not calculated
	Benign locomotor lesions	X-rays to spine and joints	< 0.2–> 0.5	Damber *et al.* (1995)	SIR, 1.07 (0.80–1.41)	Mortality	50	Dose–response not calculated
	Benign gynaecological disease	Exposure of pelvic area	(1.19)	Inskip *et al.* (1993)	RR (exposed:not), 1.1 (0.5–3.0)[a,l]	Mortality	21[l]	Dose–response not calculated
	Breast cancer	Radiation to chest, supraclavicular nodes, axilla, etc.	(5.3)	Curtis *et al.* (1989)	RR (exposed:not), 1.84 (0.5–6.7)[a]	Incidence	10	Dose–response not calculated
	Uterine corpus cancer	Radiation to vagina, pelvis and regional lymph nodes	Brachytherapy 90% range 0.7–2.7 (mean 1.7) External beam 90% range 6.4–14.0 (mean 9.7) (overall mean 5.22)	Curtis *et al.* (1994)	RR (exposed:not), 0.90 (0.4–1.9)	Incidence	54	Dose–response not calculated
	International Radiation Study of Cervical Cancer Patients	Mostly 200–400 kVp X-ray +radium +gamma to cervix	0–> 12 (7.1)	Boice *et al.* (1988)	OR, 1.03 (0.3–3.9)[a]	Incidence	52	Dose–response not calculated

Table 2.8 (continued)

Organ site	Study	Target	Dose range (mean)(Gy)	Reference	ERR/EOR per Gy/ Sv unless otherwise stated (95%CI) (A-bomb, IARC 15-country and NRRW are Sv^{-1}, all others Gy^{-1})	Mortality/ incidence	Cases/ deaths	Other comments
Chronic lymphocytic leukaemia (contd.)	Chernobyl liquidator study	Work in aftermath of Chernobyl accident	0–3.22 (0.0764)	Romanenko *et al.* (2008)	4.09 (< 0–14.41)	Incidence	39	
	Chernobyl liquidator study	Work in aftermath of Chernobyl accident	0–> 0.5 (0.013)	Kesminiene *et al.* (2008)	4.7 (–∞–76.1)[a f]	Incidence	21	
	IARC 15-country nuclear workers	Uniform whole body	0–> 0.5 Sv (0.0194)	Cardis *et al.* (2007)	–1.0 (–5.0–3.7)[a d]	Mortality	47	
	United Kingdom NRRW	Uniform whole body	0–> 0.1 Sv (0.0249)	Muirhead *et al.* (2009)	< –1.92 (< –1.92–1.23)[a] –0.12 (–1.42–2.71)[a]	Mortality Incidence	69 128	

[a] 90%CI
[b] Taken from UNSCEAR (2008b)
[c] Based on descending & sigmoid colon dose
[d] Computed using a log-linear model (central estimate and confidence bounds given as 10*(RR-1) (RR estimated at 0.1 Sv))
[e] Sex averaged
[f] Lower confidence bound not determined
[g] Based on total active red bone-marrow dose, using weights to 17 compartments defined by Christy (1981)
[h] Patients receiving less than 100 Gy to uterus were designated as controls
[I] Upper CI computed using a log-linear model
[j] Based on dose on testes
[k] Based on red bone-marrow dose
[l] Chronic lymphocytic leukaemia and lymphocytic leukaemia not otherwise specified (NOS)
CNS, central nervous system; SMR, standardized mortality ratio

(Preston *et al.*, 2003). For men, there were 172 deaths yielding an ERR/Sv of −0.25 (90%CI: < −0.3–0.15), and for women, there were 198 deaths yielding an ERR/Sv of 0.75 (90%CI: 0.16–1.6). In the analysis of incidence data, a borderline statistically significant dose–response was reported with an ERR/Sv of 0.19 (90%CI: −0.04–0.47), based on 838 cases of cancer of the rectum arising evenly between the genders (Preston *et al.*, 2007). There was a highly significant excess of cancer of the rectum in the IRSCCP ($P = 0.002$ for 10-year survivors), yielding an ERR/Gy of 0.02 (90%CI: 0.00–0.04) (Boice *et al.*, 1988). There was no statistically significant excess risk in the United Kingdom ankylosing spondylitis data (Weiss *et al.*, 1994), nor in the IARC 15-country study (Cardis *et al.*, 2007). In the latest NRRW analysis (Muirhead *et al.*, 2009), there were borderline statistically significant elevations of ERR in the mortality data (ERR/Sv, 1.69; 95%CI: −0.02–4.73), based on 303 deaths, and in the incidence data (ERR/Sv, 1.31; 95%CI: 0.04–3.2), based on 586 cases. Although the confidence intervals in the LSS, NRRW and IRSCCP overlap (as they also do with the other studies), the rather lower risks indicated in the LSS compared with the NRRW, and the even lower risks in the IRSCCP, might be explained by cell-sterilization effects.

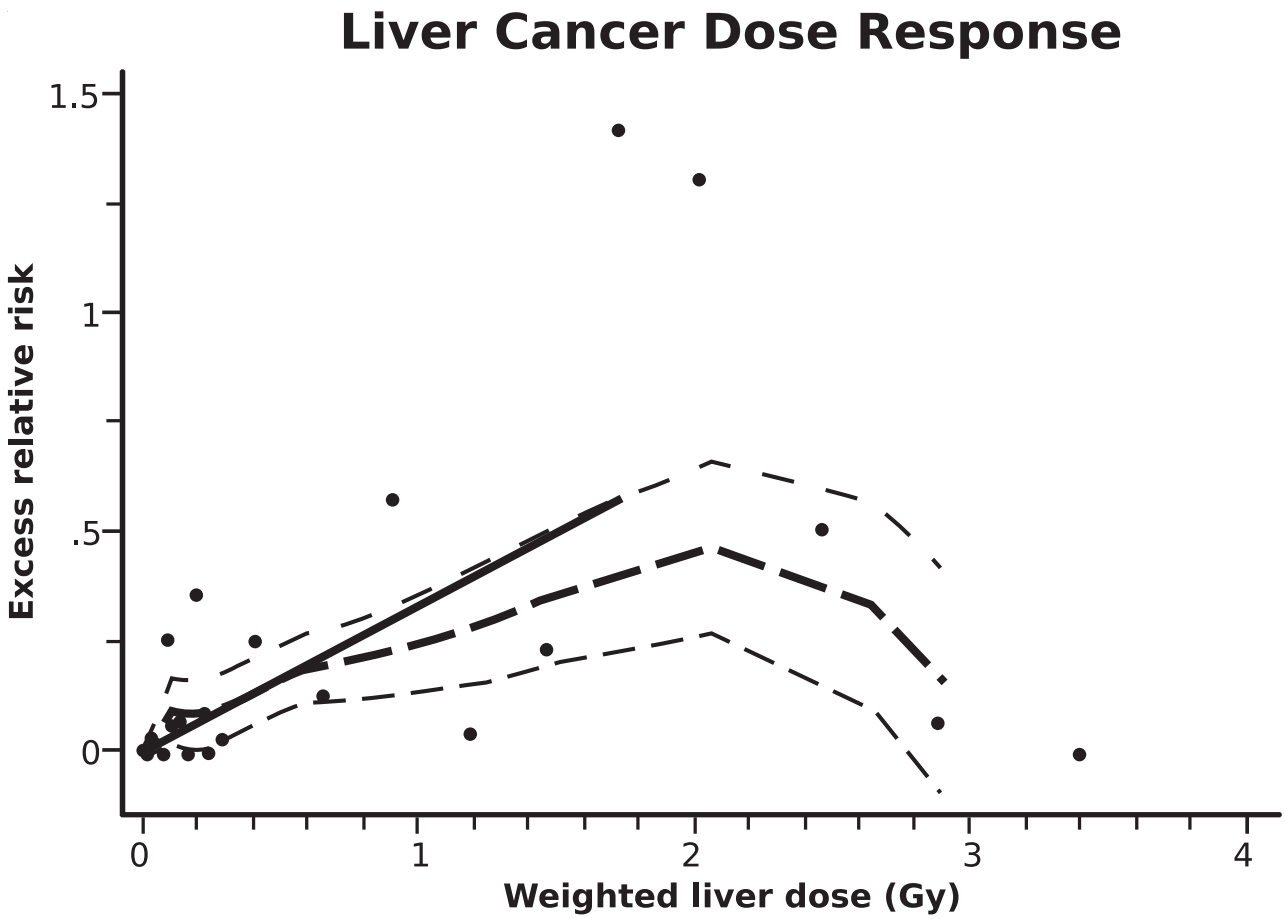
In summary, there are borderline statistically significant indications of excess risk for this cancer site in the LSS incidence data (Preston *et al.*, 2007), and for women in the LSS mortality data (Preston *et al.*, 2003). There is a significant excess risk in the IRSCCP (Boice *et al.*, 1988), but not in other medically exposed groups (Darby *et al.*, 1994; Weiss *et al.*, 1994). There are borderline statistically significant indications of excess in the NRRW (Muirhead *et al.*, 2009), but not in the IARC 15-country study (Cardis *et al.*, 2007). With only a single statistically significant positive study, chance cannot be entirely ruled out as an explanation for these results.

2.6.5 Cancer of the liver

Among the survivors of the atomic bombings, liver cancer mortality was clearly associated with radiation dose among men (Preston *et al.*, 2003). For men, 722 deaths were reported yielding an ERR/Sv of 0.39 (90%CI: 0.11–0.68); and for women, 514 deaths yielding an ERR/Sv of 0.35 (90%CI: 0.07–0.72). In the analysis of cancer incidence in the LSS, there were 1494 cases yielding a (sex-averaged) ERR/Sv of 0.30 (90%CI: 0.11–0.55; Preston *et al.*, 2007). [The Working Group noted that histological confirmation rate of these cancers was low (41%), so it is possible that a substantial number were secondary tumours, and this might also explain the scatter observed in the dose–response.] The dose–response in the incidence data implies an increase in risk at lower dose, but a reduction above about 2 Sv, with a reasonable amount of scatter around the trend line (Preston *et al.*, 2007; Fig. 2.1). There was little or no evidence of excess in most radiotherapy studies, e.g. the United Kingdom ankylosing spondylitis study of Weiss *et al.* (1994), the metropathia haemorrhagica study (Darby *et al.*, 1994), nor in any occupational studies, e.g. the IARC 15-country study (Cardis *et al.*, 2007) or the NRRW (Muirhead *et al.*, 2009). However, the numbers of cases or deaths in all these other studies is generally small.

In summary, there is strong and a statistically significant excess risk for this cancer site in the LSS incidence and mortality data (Preston *et al.*, 2003, 2007). However, the shape of the dose–response is unusual, and there appears to be a lot of noise in those data. Possibly the comparatively low percentage of cases that were histologically confirmed in the incidence data might explain this, and is a cause for concern. There was no significant excess risk in any other studies (Boice *et al.*, 1988; Darby *et al.*, 1994; Weiss *et al.*, 1994; Cardis *et al.*, 2007; Muirhead *et al.*, 2009), but the numbers of cases or deaths is small. With only a single statistically significant positive study,

Fig. 2.1 Liver cancer dose–response in the LSS incidence data



The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose–response at age 70 after exposure at age 30 based on data in the 0–2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed line is a non-parametric smooth of the category-specific estimates, and the thin dashed lines are one standard error above and below this smooth.
From Preston *et al.* (2007)

the LSS, chance cannot be entirely ruled out – it is also possible that there is contamination of the data for cancer of the liver by that for other cancer sites in the LSS.

2.6.6 Cancer of the pancreas

Among the survivors of the atomic bombings, pancreatic cancer mortality was not clearly associated with radiation dose (Preston *et al.*, 2003). The ERR/Sv was −0.11 (90%CI: < −0.3–0.44) for men, based on 163 deaths, and −0.01 (90%: −0.28–0.45) for women, based on 244 deaths. The ERR/Sv for cancer incidence in the LSS was 0.26 (90%CI: < −0.07–0.68), based on 512 cases (Preston *et al.*, 2007). The histological confirmation rate of this cancer was low (52%). A statistically significant excess risk was reported (ERR/Gy, 0.12; 95%CI: 0.05–0.20, based on 84 cases) in the United Kingdom ankylosing spondylitis data (Weiss *et al.*, 1994). There was an indication of excess risk in the Stockholm skin haemangioma study, with nine cases yielding an ERR/Gy of 25.1 (95%CI: 5.5–57.7; Lundell & Holm, 1995). The very large risk predicted by this study is statistically inconsistent with all the other studies, apart perhaps from the IARC 15-country study (Cardis *et al.*, 2007), with an ERR/Gy of 2.10 (95%CI:

–0.59–6.77), based on 272 cases. In the US peptic ulcer study of Carr *et al.* (2002), no excess risk was reported (ERR/Gy, –0.03; 95%CI: –0.10–0.05, based on 59 deaths). There was also no evidence of excess in the IRSCCP (Boice *et al.*, 1988) and in the metropathia haemorrhagica study (Darby *et al.*, 1994), nor in any occupational study, e.g. the IARC 15-country study (Cardis *et al.*, 2007) or the NRRW (Muirhead *et al.*, 2009).

In summary, there is evidence of an excess risk in the United Kingdom ankylosing spondylitis study (Weiss *et al.*, 1994) and in the Stockholm haemangioma study (Lundell & Holm, 1995); the latter was very substantial but based on a small number of cases. However, there is no significant excess risk for this cancer in the LSS incidence and mortality data (Preston *et al.*, 2003, 2007), nor in the other (radiotherapeutically or occupationally) exposed groups. With only two statistically significant positive studies, and one of these based on a small number of cases that is also inconsistent with most other studies, chance cannot be entirely ruled out, and coherence is also not well established.

2.6.7 Cancers of the bone and connective tissue

This is a rare cancer site. In most studies, cancers of the bone and connective tissues are analysed together. In most of the cohorts that were considered, bone tumours were outnumbered by connective tissue tumours. For example, in the United Kingdom NRRW, there were 17 bone cancers against 58 connective tissue cancers (Muirhead *et al.*, 2009). [The Working Group analysed the publicly available LSS incidence data set (Preston *et al.*, 2007) using a linear relative risk model,and obtained for bone and connective tissues a statistically significant ERR/Sv of 1.34 (95%CI: 0.14–3.74), based on 41 cases. The ERR/Sv was 1.01 (95%CI: < 0–4.38) for bone tumours, based on 18 cases, and 1.76 (95%CI: < 0–6.41) for connective tissues, based on 23 cases (Table 2.8).]

Significant excess risks were also reported in a group treated for retinoblastoma (ERR/Gy, 0.19; 95%CI: 0.14–0.32), based on 81 cases (Wong *et al.*, 1997; risk estimate from UNSCEAR, 2008b); in two childhood cancer cohorts of Tucker *et al.* (1987) (ERR/Gy, 0.06; 95%CI: 0.01–0.2; risk estimate from UNSCEAR, 2008b), based on 54 cases; in Hawkins *et al.* (1996) (ERR/Gy, 0.16; 95%CI: 0.07–0.37; risk estimate from UNSCEAR, 2008b), based on 49 cases; and in the United Kingdom ankylosing spondylitis cohort (RR, 3.29; 95%CI: 1.58–5.92), based on nine deaths (Weiss *et al.*, 1994). There was no significant excess risk in the IRSCCP (Boice *et al.*, 1988), nor in various occupationally exposed groups (Cardis *et al.*, 2007; Muirhead *et al.*, 2009). In these cohorts, where data were available (Boice *et al.*, 1988; Weiss *et al.*, 1994; Cardis *et al.*, 2007; Muirhead *et al.*, 2009), the risks for bone and connective tissue tumours were not markedly different, similar to the findings from the cohort of Japanese A-bomb survivors.

In summary, there is evidence of an excess risk in the LSS incidence data (Preston *et al.*, 2007) and in three other medical radiation cohorts (Tucker *et al.*, 1987; Hawkins *et al.*, 1996; Wong *et al.*, 1997). The risks in all cohorts (those with statistically significant excess or not) are also reasonably consistent. There is no evidence that risks for bone and connective tissues are dissimilar.

2.6.8 Skin cancers other than basal skin carcinoma

(a) Squamous cell carcinoma of the skin

Ron *et al.* (1998) analysed LSS incidence data and observed an ERR/Sv of –0.1 (90%CI: < –0.1–0.10), based on 69 cases (Table 2.8). Updated incidence data from LSS did not show any significant association (Preston *et al.*, 2007). Ron *et al.* (1991) observed no cases of squamous cell carcinoma in the irradiated Israeli tinea capitis group, and two in the control group. Shore *et al.* (2002) observed seven cases of squamous cell carcinoma in the

irradiated New York tinea capitis group, and none in the control group.

In summary, for this rarely studied cancer, there is essentially only a single quantitatively informative study, the LSS incidence data (Ron *et al.*, 1998), which does not indicate an excess risk. Neither of the tinea capitis cohorts (Ron *et al.*, 1991; Shore *et al.*, 2002) are quantitatively informative.

(b) Melanoma

This is a rare cancer site. In the latest analyses of A-bomb survivors' data, Preston *et al.* (2007) did not analyse this tumour, and the publicly available data were not provided. The much lower rates of this cancer in the Japanese population than observed in the western European population (Parkin *et al.*, 2002) imply that even quite large ERRs would fail to be statistically significant. [The Working Group analysed the older publicly available LSS data set (with follow-up to the end of 1987 rather than the end of 1998) of Thompson *et al.* (1994). Using a linear relative risk model, the ERR is not statistically significant (ERR/Sv, 0.22; 95%CI: < 0–4.14), based on 13 cases (Table 2.8).] There are few indications of excess risk in other groups, although a France–United Kingdom childhood cancer study yielded a statistically borderline association (excess odds ratio/Gy, 0.07; 95%CI: 0.00–0.14; Guérin *et al.*, 2003). There was no significant excess risk in the NRRW incidence data (ERR/Sv, 1.39; 95%CI: −0.65–5.6), based on 261 cases (Muirhead *et al.*, 2009), nor in the IARC 15-country study (ERR/Sv, 0.15; 90%CI: < 0–5.44), based on 87 deaths (Cardis *et al.*, 2007).

In summary, for this rarely studied cancer, there are essentially only four quantitatively informative studies, in none of which are there statistically significant excess risks. The lack of excess in the LSS is not surprising given the very low rates of this cancer in the Japanese population, even quite large ERRs would fail to be statistically significant. That said, chance cannot be excluded as an explanation of what is reported.

2.6.9 Cancer of the uterus

In the most recent analysis of cancer incidence in the LSS (Preston *et al.*, 2007), 1162 cases were reported yielding an ERR/Sv of 0.10 (90%CI: −0.09– 0.33). There was a similar (non-significant) risk in the LSS mortality data (ERR/Sv, 0.17; 90%CI: −0.10–0.52), based on 518 deaths (Preston *et al.*, 2003). There are indications in the incidence data that the risks for uterine corpus cancer (ERR/Sv, 0.29; 90%CI: −0.14–0.95) is greater than for uterine cervix cancer (ERR/Sv, 0.06; 90%CI: −0.14–0.31) [although the uncertainties are consistent with risks being equal for these two cancer sites]. There was little or no evidence of an excess in risk of uterine cancer in most radiotherapy studies, e.g. the metropathia haemorrhagica (Darby *et al.*, 1994), the IRSCCP (Boice *et al.*, 1988) or the United Kingdom ankylosing spondylitis study (Weiss *et al.*, 1994), nor in any occupational studies, e.g. the IARC 15-country study (Cardis *et al.*, 2007) or the NRRW (Muirhead *et al.*, 2009). [The occupational studies (Cardis *et al.*, 2007; Muirhead *et al.*, 2009) are particularly uninformative, for obvious reasons: there were few women in these cohorts, and women tended to have lower cumulative doses.] In the studies with subtype information, the indications, as with the LSS, are that ERRs for uterine corpus cancer are greater than for uterine cervix cancer (Weiss *et al.*, 1994; Cardis *et al.*, 2007).

In summary, for no cohort are there significant excess risks of uterine cancer. In three cohorts with subtype information (Weiss *et al.*, 1994; Cardis *et al.*, 2007; Preston *et al.*, 2007), there were common patterns in risk across studies, with greater ERRs for uterine corpus cancer than for uterine cervix cancer. The lack of excess risks in the two occupational cohorts (Cardis *et al.*, 2007; Muirhead *et al.*, 2009) is not

informative, as there were few women in those cohorts, and women tended to have lower cumulative doses.

2.6.10 Cancer of the ovary

A borderline significant excess in the incidence of cancer of the ovary (ERR/Sv, 0.61; 90%CI: 0.00–1.5), based on 245 cases (Preston *et al.*, 2007), and a similar excess of mortality (ERR/Sv, 0.94; 90%CI: 0.07–2.0), based on 136 deaths (Preston *et al.*, 2003), were reported in the LSS. There was little or no evidence of excess in most radiotherapy studies, e.g. the IRSCCP (Boice *et al.*, 1988) or the United Kingdom ankylosing spondylitis study (Weiss *et al.*, 1994), nor in any occupational studies, e.g. the IARC 15-country study (Cardis *et al.*, 2007) or the NRRW (Muirhead *et al.*, 2009; Table 2.8). [The occupational studies (Cardis *et al.*, 2007; Muirhead *et al.*, 2009) are particularly uninformative, because there were few women in those cohorts, and women tended to have lower cumulative doses. The lack of excess risk in the IRSCCP (Boice *et al.*, 1988) and metropathia haemorrhagica (Darby *et al.*, 1994) studies may partly be explained by very large doses to the ovaries, well into the range at which cell sterilization might occur.]

In summary, the only cohort with significant excess risks of ovarian cancer is the LSS. The lack of excess risks in the other studies, in particular the two occupational cohorts (Cardis *et al.*, 2007; Muirhead *et al.*, 2009), and the IRSCCP (Boice *et al.*, 1988) and metropathia haemorrhagica (Darby *et al.*, 1994) studies may not be informative, because of the low number of women, who usually had low cumulative doses, in occupational cohorts and potential cell sterilization in medical radiation cohorts.

2.6.11 Cancer of the prostate

A non-significant excess of incidence of cancer of the prostate (ERR/Sv, 0.11; 90%CI: −0.10–0.54), based on 387 cases (Preston *et al.*, 2007), and a similar excess (also lacking statistical significance) of mortality (ERR/Sv, 0.21; 90%CI: < −0.3–0.96), based on 104 deaths (Preston *et al.*, 2003), were reported in the LLS. In the United Kingdom ankylosing spondylitis data, 88 deaths were reported yielding a significant ERR/Gy of 0.14 (95%CI: 0.02–0.28; Weiss *et al.*, 1994). There was a non-significant excess of mortality from cancer of the prostate in occupational studies, e.g. the IARC 15-country study (Cardis *et al.*, 2007) or the NRRW (Muirhead *et al.*, 2009; Table 2.8).

In summary, the only cohort with significant excess risks of cancer of the prostate is the ankylosing spondylitis cohort. The risks in the other studies, although not statistically significant, are not incompatible with those in this cohort.

2.6.12 Cancer of the urinary bladder

Significant excess risk for cancer of the urinary bladder in the LSS has been reported in the most recent analysis of cancer incidence (ERR/Sv, 1.23; 90%CI: 0.59–2.1; Preston *et al.*, 2007) and of mortality with an ERR/Sv of 1.1 (90%CI: 0.2–2.5) for men and 1.2 (90%CI: 0.10–3.1) for women (Preston *et al.*, 2003). Significant excess risks were also reported from the United Kingdom ankylosing spondylitis data (ERR/Gy, 0.24; 95%CI: 0.09–0.41), based on 71 deaths (Weiss *et al.*, 1994), and the IRSCCP study (ERR/Gy, 0.07; 90%CI: 0.02–0.17), based on 273 cases (Boice *et al.*, 1988). [The Working Group noted that although the risk estimated in the last two cohorts are lower than those in the LSS, cell sterilization resulting from the somewhat higher average doses might explain this difference.] The metropathia haemorrhagica study (Darby *et al.*, 1994) suggests quite high risks (SMR, 3.01; 95%CI: 1.84–4.64) based on 20 deaths (average

dose, 5.2 Gy), and the ERR/Gy was 0.40 (95%CI: 0.15–0.66). There was no significant excess in any occupational study, e.g. the IARC 15-country study (Cardis *et al.*, 2007) or the NRRW (Muirhead *et al.*, 2009; Table 2.8).

In summary, there is strong evidence of excess risk in the LSS incidence and mortality data (Preston *et al.*, 2003, 2007), and in three other medical radiation cohorts (Boice *et al.*, 1988; Darby *et al.*, 1994; Weiss *et al.*, 1994). The risks in all cohorts (those with statistically significant excess or not) are all reasonably consistent.

2.6.13 Cancer of the kidney

Preston *et al.* (2007) analysed renal cell carcinomas (comprising 68% of the kidney cancers) in the LSS incidence data set, and obtained a non-significant ERR/Sv of 0.13 (90%CI: −0.25–0.75), based on 167 cases (Table 2.8). However, there were indications that ERR significantly decreased with either increasing age at exposure ($P = 0.005$) or with increasing attained age ($P < 0.001$). For this reason Preston *et al.* (2007) also fitted an absolute risk model, yielding a statistically significant dose–response EAR of 0.25×10^{-4} person–year Sv (90%CI: 0.07–0.53). There were similar, although non-significant, excess risks in the most recent LSS analysis of mortality (Preston *et al.*, 2003)—for men, there were 36 deaths resulting in an ERR/Sv of −0.02 (90%CI: < −0.3–1.1), and for women, there were 31 deaths and an ERR/Sv of 0.97 (90%CI: < −0.3–3.8). In the United Kingdom ankylosing spondylitis data, there were 35 deaths yielding a significant ERR/Gy of 0.10 (95%CI: 0.02–0.20) (Weiss *et al.*, 1994). There is also a significant excess in the IRSCCP (Boice *et al.*, 1988); 148 cases resulting in a significant ERR/Gy of 0.71 (90%CI: 0.03–2.24). There was no significant excess in any occupational study, e.g. the IARC 15-country study (Cardis *et al.*, 2007) or the NRRW (Muirhead *et al.*, 2009; Table 2.8).

In summary, there is evidence of excess risk in the LSS incidence data (Preston *et al.*, 2007) and in two other medical radiation cohorts (Boice *et al.*, 1988; Weiss *et al.*, 1994). The risks in all cohorts (those with statistically significant excess or not) are all reasonably consistent.

2.6.14 Cancer of the brain and central nervous system

In the most recent analysis of cancer incidence in the LSS (Preston *et al.*, 2007), there were 281 cases resulting in a significant ERR/Sv of 0.62 (90%CI: 0.21–1.2). In the LSS mortality analysis, there were very large and significant excess risks for men (ERR/Sv, 5.3; 90%CI: 1.4–16) based on 14 deaths (Preston *et al.*, 2003). For women, there were 17 deaths yielding a more modest ERR/Sv of 0.51 (90%CI: < −0.3–3.9). In the New York tinea capitis study, there was also a significant association (ERR/Gy, 1.1; 95%CI: 0.1–2.8), based on seven cases (Shore *et al.*, 2003). In the Israeli tinea capitis study, there were also significantly raised risks of both malignant brain tumours (ERR/Gy, 1.98; 95%CI: 0.73–4.69; based on 44 cases) and benign meningiomas (ERR/Gy, 4.63; 95%CI: 2.43–9.12; based on 81 cases), with a stronger increase in risk for benign brain tumours (Sadetzki *et al.*, 2005). A similar pattern of risks was seen in the France–United Kingdom childhood cancer study; the ERR/Gy was 0.07 (95%CI: < 0–0.62) based on 12 cases for malignant lesions, and > 1000 (95%CI: 0.25– > 1000) based on ten cases for benign lesions; (Little *et al.*, 1998). In the United Kingdom ankylosing spondylitis data, there was one spinal cord death resulting in a significant ERR/Gy of 3.33 (95%CI: 0.08–18.6; Weiss *et al.*, 1994). There is no significant excess in any occupational study, e.g. the IARC 15-country study (Cardis *et al.*, 2007) or the NRRW (Muirhead *et al.*, 2009; Table 2.8).

In summary, there is evidence of significant excess brain and central nervous system tumour risk in the LSS incidence data (Preston *et al.*, 2007), in two tinea capitis cohorts (Shore *et al.*, 2003; Sadetzki *et al.*, 2005), in an ankylosing

spondylitis cohort (Weiss *et al.*, 1994) and in the France–United Kingdom childhood cancer study (Weiss *et al.*, 1994). A similar pattern of excess risk being higher for benign tumours than for malignant is in the Israeli tinea capitis and France–United Kingdom cohorts. The risks in all cohorts (those with statistically significant excess or not) are all reasonably consistent.

2.6.15 Non-Hodgkin lymphoma

In the analysis of haematological malignancy incidence in the LSS cohort (Preston *et al.*, 1994), there was a borderline significant EAR of 0.56×10^{-4} /person–years /Sv (90%CI: 0.08–1.39) for men, but this was not true for women (EARx10^{-4}/person–year /Sv, 0; 90%CI: < 0–0.28). [Fitting a simple linear relative risk model, overall there was no significant excess risk (ERR/Sv, 0.05; 90%CI: < 0–0.70).] These incident findings are consistent with the analysis of male adult LSS mortality data, with a reported ERR/Sv of 1.12 (90%CI: 0.26–2.51) based on 84 cases (Richardson *et al.*, 2009). In the United Kingdom ankylosing spondylitis cohort, there were 37 deaths yielding a significant relative risk of 1.74 (95%CI: 1.23–2.36; Weiss *et al.*, 1994); there was no dose–response analysis in this cohort. There was no significant excess risk in the IRSCCP (Boice *et al.*, 1988), in the metropathia haemorrhagica cohort (Darby *et al.*, 1994), or in a group treated for benign gynaecological disease (Inskip *et al.*, 1993; Table 2.8). Among occupational studies, there was a very large excess risk in a cohort of Chernobyl liquidators (ERR/Gy, 28.1; 90%CI: 0.9–243) based on 20 cases (Kesminiene *et al.*, 2008), and in the cohort of Savannah River Site workers (ERR/Gy, 7.62; 90%CI: 0.93–20.77) based on 51 cases (Richardson *et al.*, 2009). However, there was no significant excess risk in the IARC 15-country study (ERR/Sv, 0.44; 90%CI: < 0–4.78) based on 248 deaths (Cardis *et al.*, 2007), or in the NRRW cohort (ERR/Sv, 1.28; 95%CI: −0.38–4.06) based on 305 cases (Muirhead *et al.*, 2009).

In summary, there is evidence of a significant excess risk of non-Hodgkin lymphoma in men (but not women) in the LSS mortality and incidence data (Preston *et al.*, 2003, 2007), in a cohort of Chernobyl liquidators (Kesminiene *et al.*, 2008) and in the Savannah River Site workers (Richardson *et al.*, 2009).

2.6.16 Hodgkin disease

Preston *et al.* (1994) in the LSS did not analyse this tumour. [The Working Group analysed the publicly available data set using a linear relative risk model, and obtained a non-significant ERR/Sv of 0.48 (95%CI: < 0–3.96), based on 21 cases (Table 2.8).] In the United Kingdom ankylosing spondylitis data, there were 13 deaths yielding a non-significant relative risk of 1.65 (95%CI: 0.88–2.81; Weiss *et al.*, 1994); no dose–response analysis was reported. There was no significant excess in the IRSCCP (Boice *et al.*, 1988), in the metropathia haemorrhagica cohort (Darby *et al.*, 1994), in a group treated for benign gynaecological disease (Inskip *et al.*, 1993), in the IARC 15-country study (Cardis *et al.*, 2007), or in the NRRW (Muirhead *et al.*, 2009; Table 2.8). [The Working Group noted that a common feature of all the cohorts is the small number of cases, so that large ERRs would be required to detect a significant excess in these groups.]

In summary, there are no cohorts with significant excess risks for Hodgkin disease. However, the small number of cases in all groups mean that a large ERR would be required to detect significant excess risks.

2.6.17 Multiple myeloma

In the most recent analysis of haematological malignancy incidence in the LSS, Preston *et al.* (1994) used an absolute risk model and obtained a non-significant EAR (EAR/10^4 person–year

Sv, 0.08; 95%CI: < 0–0.3), based on 59 cases (Table 2.8). In the United Kingdom ankylosing spondylitis data, there were 22 deaths yielding a borderline significant relative risk of 1.62 (95%CI: 1.07–2.46; Weiss *et al.*, 1994); there was no dose–response analysis in this cohort due to a lack of appropriate organ dose. There was a significant excess risk in the metropathia haemorrhagica cohort with an SMR of 2.59 (95%CI: 1.19–4.92), based on nine deaths (Darby *et al.*, 1994). There was no significant excess risk in the IRSCCP (Boice *et al.*, 1988), and in a group treated for benign gynaecological disease (Inskip *et al.*, 1993). There was also no excess risk in the IARC 15-country study (Cardis *et al.*, 2007). There was a highly significant excess in the incidence of multiple myeloma in the NRRW (ERR/Sv, 3.60; 95%CI: 0.43–10.37), based on 149 cases; and there was an excess of much smaller size (which was non-significant) for mortality in that cohort (ERR/Sv, 1.20; 95%CI: –1.08–7.31), based on 113 deaths (Muirhead *et al.*, 2009; Table 2.8).

In summary, there is no evidence of an excess risk of multiple myeloma in the LSS incidence data (Preston *et al.*, 1994), although an excess risk has been reported from the NRRW study (only incidence and not mortality; Muirhead *et al.*, 2009), and also from the ankylosing spondylitis study (Weiss *et al.*, 1994) and from the metropathia haemorrhagica study (though based only on analysis of SMR) (Darby *et al.*,1994).

2.6.18 Chronic lymphocytic leukaemia

Most of the information on this tumour comes from occupationally and medically exposed groups. There are very few chronic lymphocytic leukaemias in the LSS cohort – only four were documented in the latest reported analysis of haematological malignancy incidence (Preston *et al.*, 1994). In general, this is a much less common tumour in the Japanese population than in the European population. In all occupational cohorts, there were no significant excess. For example, the ERR/Sv for the incidence of chronic lymphocytic leukaemia in the NRRW was –0.12 (90%CI: –1.42–2.71), based on 128 cases (Muirhead *et al.*, 2009; Table 2.8). In the IARC 15-country study, there was an ERR/Sv of –1.0 (95%CI: –5.0–3.7), based on 47 deaths (Cardis *et al.*, 2007). In the two Chernobyl liquidator studies (Kesminiene *et al.*, 2008; Romanenko *et al.*, 2008), the risks are both large and positive, although in neither case conventionally statistically significant. For example, the ERR/Gy in the study by Kesminiene *et al.* (2008) was 4.7 (90%CI: –∞–76.1), based on 21 cases (Table 2.8). In medically exposed groups, there was no indication of excess risk in the benign gynaecological disease cohort of Inskip *et al.* (1993) (RR, 1.1; 90%CI: 0.5–3.0; based on 21 deaths), in a group irradiated for benign locomotor lesions (SIR, 1.07, 90%CI: 0.80–1.41; based on 50 deaths; Damber *et al.*, 1995), in the IRSCCP (OR, 1.03, 90%CI: 0.3–3.9; based on 52 cases; Boice *et al.*, 1988), and in many other medically irradiated groups (Curtis *et al.*, 1989, 1994, Weiss *et al.*, 1994).

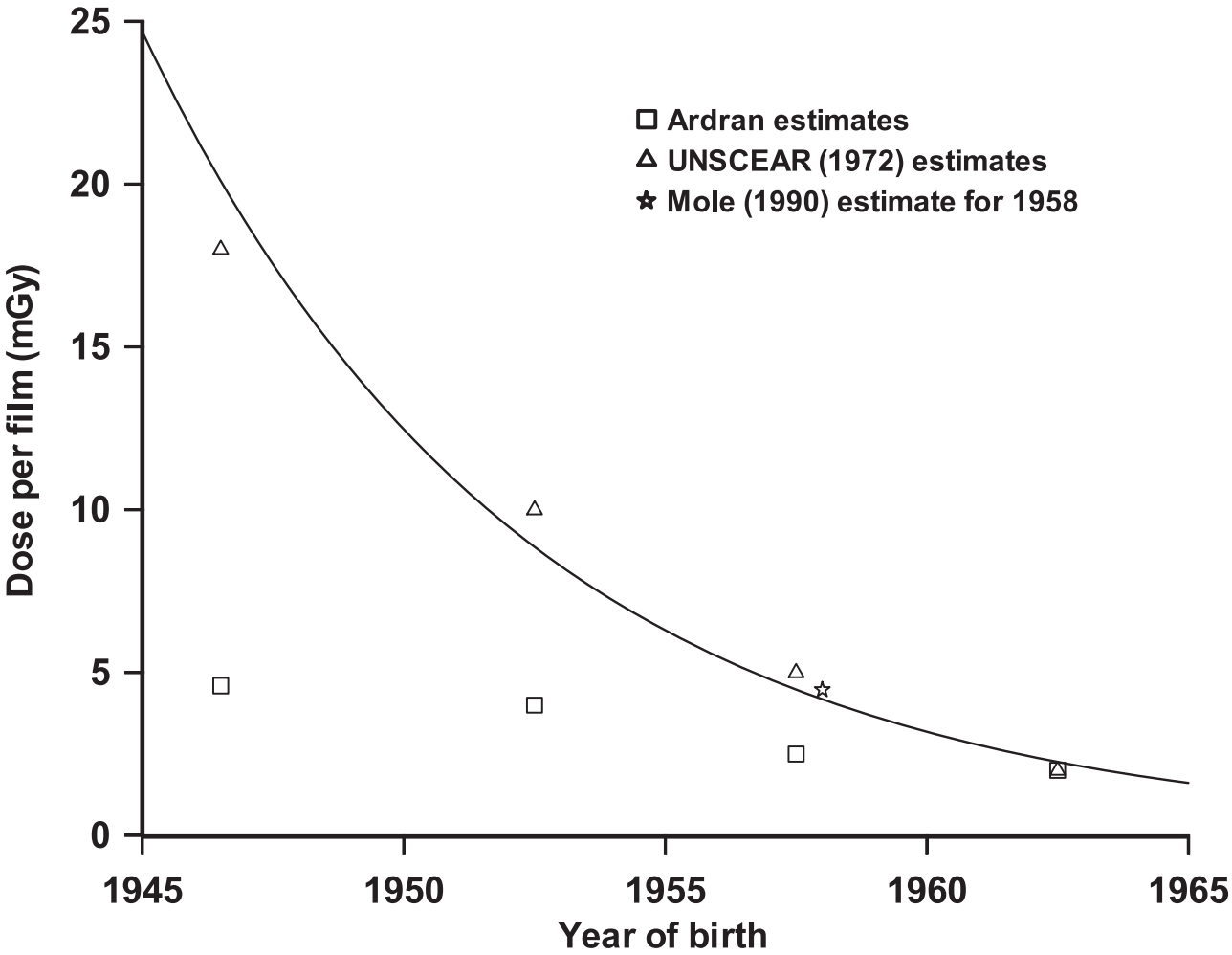
In summary, there is remarkably little evidence of a significant excess risk of chronic lymphocytic leukaemia in a large number of studies.

2.6.19 Exposure in utero

Preston *et al.* (2008) reported statistically significant dose-related increases in incidence rates of solid cancers among A-bomb survivors exposed to radiation *in utero* (see Section 2.1.3).

Excess cancer risk associated with diagnostic X-ray exposure was reported in the Oxford Survey of Childhood Cancers (Bithell & Stewart, 1975), and in various other groups exposed *in utero* (Stewart *et al.*, 1958; Monson & MacMahon, 1984; Harvey *et al.*, 1985). However, the interpretation of these in-utero studies remains controversial (Boice & Miller, 1999; ICRP, 2003), in particular because the risk for most childhood solid tumour types is increased, at about 40%, by the

Fig. 2.2 Estimates of average fetal dose per film exposed in an obstetric X-ray examination

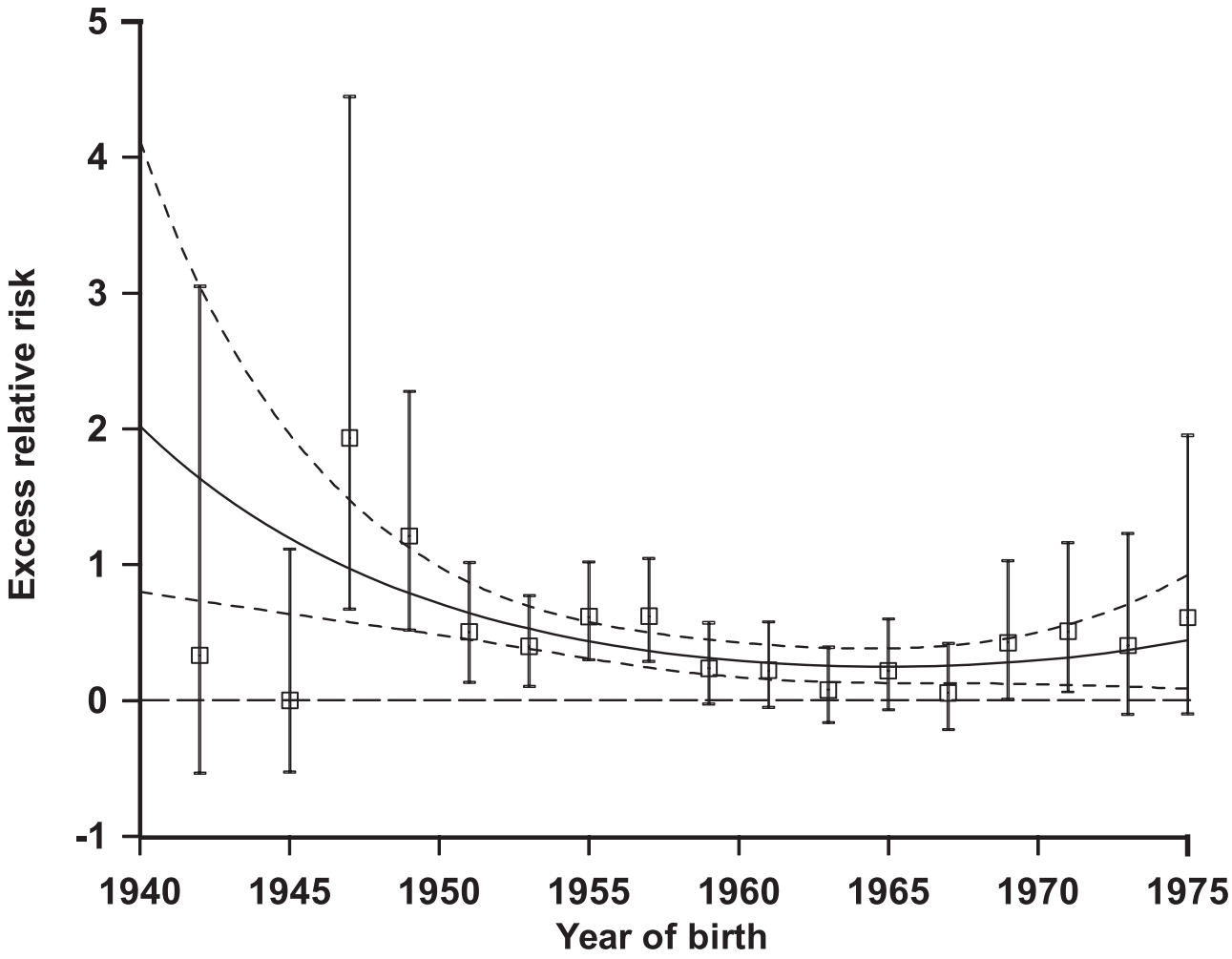


Carried out in four successive periods (1943–49, 1950–54, 1955–59, 1960–65), by Ardran (Stewart & Kneale, 1970) and UNSCEAR (1972); also shown is the estimate for 1958 (4.47 mGy) by Mole (1990) from the Adrian Committee data. The curve represents the fit of a log-linear model to the UNSCEAR (1972) dose estimates (see Bithell & Stiller, 1988) (reproduced from Wakeford & Little, 2003).

same magnitude as that for childhood leukaemia (see Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-02-Table2.9.pdf), implying a possible bias. However, eight cancers among those exposed in childhood and *in utero* in the Japanese A-bomb survivors developed in adolescence (ages 14–19 years), and were of various types (Preston *et al.*, 2008). The seven of this group that developed after childhood exposure included tumours of the stomach, bone, soft tissue, skin, thyroid and two tumours of the central nervous system. The single tumour in this age group that developed after in-utero exposure was a Wilms tumour diagnosed at the age of 14 years (Preston *et al.*, 2008). This spectrum of tumours after early childhood exposure suggests that the lack of specificity in the spectrum of tumours in the in-utero medical exposure cohorts is not necessarily remarkable.

It has been suggested that the general elevation in risk of most cancer types in the in-utero medically exposed groups is related to recall bias or confounding, possibly by some factors operating in pregnancy that had given rise to the need for radiographic examination. Recall bias has been more or less excluded by cohort studies

Fig. 2.3 The variation of the excess relative risk of childhood cancer associated with an obstetric X-ray examination by year of birth (1940–76) within the Oxford Survey of Childhood Cancers



Data are taken from Mole (1990), with 95%CIs; the curve (solid line) represents the fit of a log-linear-quadratic model to the data, with 95%CI (short dashed lines) similar to that fitted by Bithell (1993). The long dashed horizontal line indicates zero excess relative risk (reproduced from Wakeford & Little, 2003).

in which similar risks are observed (MacMahon, 1962; Monson & MacMahon, 1984), also by the high degree of confirmation of mothers' recalled exposures by medical records (Knox *et al.* 1987). Moreover, the idea that the association might be due to confounding became less plausible after the Oxford Survey of Childhood Cancers (Mole, 1990), which showed quantitatively similar relationships (risks per film) in singletons and twins, despite the fact that 55% of twins had received diagnostic exposures compared with 10% of singletons. The lack of indication of excess risk in earlier studies among the in-utero exposed Japanese A-bomb survivors has also been cited as a difficulty in interpreting the indications of excess in the medically exposed groups to be causal (Boice & Miller, 1999). However, there is a statistically significant excess risk of solid cancers after in-utero and early childhood radiation exposure (age < 6 years at exposure) in the children and adults (at ages 12–55 years) in the Japanese A-bomb survivors (Preston *et al.*, 2008) with a strong decline in ERR with attained age, which is consistent with results of the Oxford

Survey of Childhood Cancers. Although there are no leukaemia cases in the Japanese in-utero cohort in childhood (there were two cases at a later age, Yoshimoto *et al.*, 1994), the lack of excess is nevertheless consistent with the excess risk observed in the Oxford Survey of Childhood Cancers, and in other in-utero medically irradiated groups (Wakeford & Little, 2003). The lack of cases among the Japanese and possible inconsistency with some of other groups may also be plausibly accounted for by cell-sterilization effect (Little, 2008). The fact that risk reduces with calendar time, almost exactly paralleling the reduction in in-utero dose (see Fig. 2.2 and 2.3) substantially increases the plausibility of the observed association in the medical groups (Doll & Wakeford, 1997; Wakeford & Little, 2003), as does the dose–response relationship observed in the Oxford Survey of Childhood Cancers (Bithell, 1993). A meta-analysis, which covered only studies published after 1990, did not find any association between in-utero medical radiation and risk of childhood cancer (Schulze-Rath *et al.*, 2008). [The Working Group noted that because in-utero diagnostic doses are substantially lower than those in the 1950s discussed above, the findings of this meta-analysis may not be comparable with those of the earlier medical in-utero studies.]

In summary, there is substantial evidence that suggests a causal association between exposure to diagnostic radiation *in utero* and childhood cancers. This association is supported by the fact that the Japanese A-bomb survivors exposed *in utero* and in early childhood are at higher risk for a wide range of solid cancers in adulthood, and that risks among the in-utero and childhood-exposed groups are very similar. This indicates that the increased risk of cancer following in-utero exposure to radiation starts in childhood, and persists long into adulthood.

3. Cancer in Experimental Animals

3.1 Previous evaluation

Both X-rays and γ-rays have been shown to increase the risk for the development of a variety of cancers in experimental animals. This work was extensively reviewed in the previous *IARC Monograph*, which covered work up to the year 2000 (IARC, 2000).

X-rays and γ-rays have been tested for carcinogenicity at various doses and under various conditions in mice, rats, rabbits, dogs, and rhesus monkeys. They have also been tested by exposure of mice and dogs *in utero*, and by parental exposure of mice (IARC, 2000).

In adult animals, the incidences of leukaemia and of a variety of neoplasms including mammary, lung and thyroid tumours were increased in a dose-dependent manner with both types of radiation. In mice, X-rays and γ-rays clearly increased the incidence of myeloid leukaemia, malignant lymphoma (including thymic lymphoma), malignant tumours of the ovary, and lung and mammary adenocarcinomas (Upton *et al.*, 1970; Ullrich & Storer, 1979a, b, c; Ullrich, 1983; Ullrich & Preston., 1987; Grahn *et al.*, 1992; IARC, 2000). Benign and malignant tumours of the liver, Harderian gland, pituitary gland, and adrenal gland were also induced (Ullrich & Storer, 1979b, c; Grahn *et al.*, 1992; IARC, 2000). In rats, X-rays and γ-rays clearly increased the incidence of malignant mammary tumours (Shellabarger *et al.*, 1966, 1980; Broerse *et al.*, 1986, 1987; IARC, 2000) and of follicular carcinomas of the thyroid (Lee *et al.*, 1982; IARC, 2000). In rhesus monkeys, X-rays clearly increased the incidence of kidney adenocarcinomas (Broerse *et al.*, 1981). When enough data were available over a range of doses and dose rates, the dose–response relationship was generally consistent with a linear–quadratic model, while lowering the dose rate resulted in a diminution of the quadratic portion of the curve. The effects of

fractionation of the dose were highly dependent on fractionation size. Most importantly, low-dose fractions were equivalent to low-dose rates with respect to carcinogenic effectiveness (IARC, 2000).

Prenatal exposure of mice to X-rays in two studies and to γ-rays in one study and of dogs to γ-rays at late fetal stages resulted in significant increases in the incidences of malignant lymphoma (Lumniczky *et al.*, 1998), malignant lung and liver tumours in mice (Sasaki *et al.*, 1978a, b; IARC, 2000), and malignant lymphoma, haemangiosarcoma and mammary carcinoma in dogs (Benjamin *et al.*, 1991; IARC, 2000). Exposure at early fetal stages, however, did not increase the incidence of tumours in the offspring of either species (IARC, 2000).

Parental effects in mice appear to depend on the strain tested. Parental exposure of mice of two strains to X-rays resulted in increased incidences of lung adenomas and lymphocytic leukaemias in the offspring; however, studies with other strains of mice showed no increase in the incidence of neoplasms (IARC, 2000).

3.2 Studies published since the previous *IARC Monograph*

The following text (see also Table 3.1) provides an update of studies published since that time. Most studies published over the period 2001 to 2009 have examined effects of X-rays and γ-rays in adult rodents (mice and rats). In particular, the majority of mouse studies have focused on the use of genetically engineered mouse model systems.

3.3 Studies in adult animals

3.3.1 Mouse

Studies in adult mice have focused on the effects of low doses and dose rates in an attempt to provide more information that could provide insight into risks at doses for which data for humans is not sufficient to establish the shape of the dose–response realtionship.

Di Majo *et al.* (2003) published a summary of several series of studies conducted over several years examining the carcinogenic effects of ionizing radiation. This summary was meant to examine the dose response at low doses using a synthesis of data from previously conducted studies. This paper did not present new data but rather presented a different analysis. Only a small portion of this paper described data for X-radiation, with most examining effects of neutrons. For X-radiation, cancer development was analysed in female B6C3F1 mice irradiated at 1 month of age with doses of 40, 80, 160 and 320 mGy of 250 kVp X-rays. The sample sizes ($n = 52–97$) were quite small but the data provided limited evidence for an increase in cancer risks. No increase in the incidence of lymphomas or myeloid leukemias was observed at any dose used. For solid tumours, an apparent decrease in frequency was observed at the 40 mGy dose, and at higher doses there was a slight but not significant increase at 80 and 160 mGy with little evidence of a dose response. For ovarian tumours, significant increases were found at doses of 80, 160, and 320 mGy.

A large study of effects of very low dose rates of γ-rays was conducted by Tanaka and co-workers (Tanaka *et al.*, 2007) using 4000 B6C3F1 mice (8 weeks of age). These mice were irradiated with γ-rays at dose rates of 0.05, 1.1, and 21 mGy per day over a 400-day time period, which resulted in total doses of 20, 400, and 8000 mGy. A previous report on life-shortening (Tanaka *et al.*, 2003) had found an increase in life-shortening at the 21 mGy per day dose rate (8000 mGy total dose) in males, but no effect at lower doses or dose rates and an increase in females exposed at 1.1 and 21 mGy per day dose rates (400 and 8000 mGy) but not following 0.05 mGy per day (20 mGy total dose) in females. The 2007 study on neoplasia found significant increases in

Table 3.1 Studies in experimental animals exposed to X- and γ-rays identified since the previous *IARC Monograph* (IARC, 2000)

Species, strain (sex) Duration Reference	Number/group at start Dosing regimen	Incidence of tumours	Significance
Mouse, B6C3F1, (F) Lifespan Di Majo *et al.* (2003)	Acute exposure 0, 40, 80, 160, 320 mGy (250 kVp X-rays) 52–97; 335 controls	Solid tumours (%): 38.2, 34.0, 45.6, 46.2, 39.3 Ovarian tumours (%): 9.9, 9.3, 20.3[a], 59.6[b], 80.4[b]	[a]$P \leq 0.01$ (Fisher test) [b]$P \leq 0.001$ (Peto's trend test)
Mouse, B6C3F1, (M, F) Lifespan Tanaka *et al.* (2007)	0, 20, 400, 8000 mGy ^{137}Cs (total dose) 0.05, 1.1, 21 mGy/d 495–500; 498 controls	*Males:* Myeloid leukaemia– 7/498 (1%); 10/495 (2%); 10/500 (2%); 24/499 (5%) [a, b] Hemangiosarcomas– 5/498 (1%); 51/495 (10%); 62/500 (12%); 84/499 (17%) [b] *Females:* Hemangiosarcomas– 21/500 (4%); 21/495 (4%); 32/497 (6%); 47/500 (9%) [a, b] Ovarian tumours (malignant granulosa cell)– 1/500 (0.2%); 2/495 (0.4%); 0; [a, 13/500 (2.6%) [b]	[a]$P \leq 0.01$ (Fisher test) [b]$P \leq 0.001$ (Peto's trend test)
Mouse, Car-R and Car-S, (M) Pazzaglia *et al.* (2002a)	Car-S: 4 weekly doses of 0, 1500, 2000, 2500 mGy plus TPA Car-R: 4 weekly doses of 2000, 5000 mGy TPA 1 µg was given 7 d after the last irradiation biweekly for 200 d to all groups 26–35; 94 controls	Skin tumours (%): Car-S–25.5,54.5,28.6,58.3 Car-R–0,0	$P < 0.001$ (in all groups)
Mouse, Min (M, F) Lifespan Okamoto & Yonekawa (2005)	0, 250, 500, 1000, 2000 mGy X-rays 1000, 2000 mGy at 2-, 10-, 24-, 42-, 48-d-old Number/group at start (NR)	Small intestine (~multiplicity): 77.6, 120, 125, 150, 207 Colon (~multiplicity): 3.5, 2.5, 2.8, 6.3, 16.8 *Age (days)* Small intestine (~multiplicity): 2 d–125, 160 10 d–148, 210 24 d–140, 160 42 d–77, 125 48 d–NR, 80	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Number/group at start Dosing regimen	Incidence of tumours	Significance
Mouse, C57BL/6, C57Bl/6-Min (F) 18 wk Imaoka *et al.* (2006)	0, 2000 mGy X-rays at 2-, 5-, 7-, 10-wk-old Number/group at start (NR)	Mammary tumours (adenoacanthomas): C57Bl/6 0 at all doses Controls–2/10 (20%) 2 wk–2/7 (29%) 5 wk–2/13 (15%) 7 wk–7/11 (64%) [c] 10 wk–6/9 (67%) [c]	[c] $P < 0.002$ compared to wild type; $P < 0.05$ compared to 0 mGy
Mouse, Min *Prkdc*$^{BALB/BALB}$, Min *Prkdc* $^{BALB/C57BL}$ (M, F) Degg *et al.* (2003)	0, 2000 mGy X-rays 84 M, 58 F; controls 60 M, 51 F	Small intestine (multiplicity): Min *Prkdc*$^{BALB/BALB}$–20.9, 51.7 Min *Prkdc*$^{BALB/C57BL}$–29.4, 37.1	
Mouse, *Apc* $^{Min/+}$ (F, F) CBA/F (F) Ellender *et al.* (2006)	0 or 2000 mGy X-rays at 2-, 10-, 35-d-old 0, 500, 1000, 2000 mGy at 7 days post conception (PC) (pregnant CBA/H mice) 50/group	Intestinal tumours: incidence Controls–27.8 2 d–85.2 [d e] 10 d–125.5 [d f] 35 d–71.3 [d] 7 d PC–29.9, 35.6, 34.3, 37.0	[d] $P < 0.001$ compared to controls; [e] $P = 0.02$ compared to 35 days [f] $P < 0.001$ compared to 35 days
Mouse, C57BL, C57BL *Apc*$^{min/+}$ Nakayama *et al.* (2007)	0, 5000 mGy X-rays Controls; wild type 13 M, 18 F; *Apc*$^{min/+}$ 32 M, 32 F, killed after 28 wk X-rays: wild type 13 M, 16 F; *Apc*$^{min/+}$ 44 M, 33 F, killed after 20 wk	Intestinal tumours (multiplicity): M–9/32 (28%); 24/44 (55%)[g] F–4/32 (13%); 16/33 (49%)[h] Mammary tumours (%): 1/32 (3%); 10/33 (30%)[i]	[g] $P < 0.05$ vs control *Apc*$^{min/+}$ [h] $P < 0.005$ vs control Apc$^{min/+}$ [i] $P < 0.01$ vs control *Apc*$^{min/+}$
Mouse, C57BL wild type and *Apc*1638N, (M, F) van der Houven van Oordt *et al.* (1997)	0, 5000 mGy X-rays Controls: Apc1638N 19 M, 8 F, killed at 6–16 mo X-rays: wild type 15 M, 24 F; Apc1638N 15 M, 16 F killed after 250 d	Intestinal tumours (multiplicity): Wild type–0, 0 *Apc*1638N–2.7, 21.0 Mammary tumours (%): Wild type–0, 0 *Apc*1638N–0, 63	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Number/group at start Dosing regimen	Incidence of tumours	Significance
Mouse, B6,A/JB6F1,CB6F1,C3B6F1 (M, F) van der Houven van Oordt *et al.* (1999)	0, 5000 mGy X-rays Controls: Apc1638N 30–41/group, Apc+ 11–30/group X-rays: Apc1638N 21–34/group, Apc+ (non-transgenic) 25–29/group killed at 26 wk of age	Intestinal tumours (multiplicity): B6–2.9, 29.6 A/JB6F1–1.4, 9.1 CB6F1–1.2, 14.6 C3B6F1–3.1, 51.0 Mammary tumours (%): B6–0, 6/12 (50%) A/JB6F1–0, 7/18 (39%)[j] CB6F1–1/15 (7%); 3/12 (25%)[k] C3B6F1–1/15 (7%); 0	 [j]$P = 0.007$ vs untreated [k]$P = 0.002$ vs untreated NS
Mouse, 129/SV *Ptch1*$^{+/+}$ and $^{+/-}$ (M, F) 38 wk (treated at 4 d) 72 wk (treated at 3 mo) Pazzaglia *et al.* (2002b)	0, 3000 mGy X-rays 4 d or 3 mo of age At 4 d: controls–31 *Ptch1*+/–, *Ptch1* 26 +/+ X-rays–51 *Ptch1*+/–, *Ptch1*46 +/+ At 3 mo: controls–30 *Ptch1*+/–, 22 *Ptch1*+/+ X-rays–41 *Ptch1*+/–, 43 *Ptch1*+/+	Medulloblastomas (%): At 4 d– Controls *Ptch1*+/– 5/31 (16.12%) Controls *Ptch1*+/+ 1/26 (3.2%) X-rays *Ptch1*+/– 38/51 (74.5%) X-rays *Ptch1*+/+ 14/46 (30.4) At 3 mo– Controls *Ptch1*+/– 15/30 (50%) Controls *Ptch1*+/+ 0 X-rays *Ptch1*+/– 21/41 (51.2%) X-rays *Ptch1*+/+ 6/43 (14%)	 NR NR
Mouse, 129/SV *Ptch1*$^{+/+}$ and $^{+/-}$ (M, F) 60–90 wk Mancuso *et al.* (2004)	0, 3000 mGy X-rays whole body at 4 d of age or 90 d of age or 4000 mGy localized to dorsal skin at 60 d of age controls: 52 *Ptch1*+/+, 52 *Ptch1* +/– 4 d: 46 *Ptch1*+/+, 52 *Ptch1*+/– 90 d: 40 *Ptch1*+/+, 39 *Ptch1*+/– 60 d: 56 *Ptch1* +/+, 61 *Ptch1*+/–	Nodular basal cell carcinomas (%) in heterozygous: Controls–0; 9/33 (27%) 4 d–0; 11/46 (24%)[l] 90 d–0; 15/32 (47%)[l] 60 d–0; 29/47 (62%)[l] Infiltrative basal cell carcinomas: controls–NR 4 d–0; 2/52 (4%) 90 d–0; 4/33 (12%)[l] 60 d–0; 3/61 (5%)	 [l]$P < 0.05$ [l]$P < 0.05$

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Number/group at start Dosing regimen	Incidence of tumours	Significance
Mouse, F1S*Ptch1* wild type, F1S *Ptch1*$^{neo67/+}$, F1R*Ptch1* wild type, F1R*Ptch1* $^{neo67/+}$ (M, F) Lifespan Pazzaglia *et al.* (2004)	0, 4000 mGy X-rays local to 60-d-old mice or 3000 mGy whole body to 4–8-d-old mice controls: F1S–59 +/+, 39 +/– F1R–24 +/+, 25 +/– 60 d: F1S–72 +/+, 65 +/– F1R–28 +/+, 28 +/– 4–8 d: F1S–46 +/+, 32 +/– N2 CarsS–25 +/+, 16 +/–	Medulloblastomas: 4-d-old mice– F1S 1/39 (2.6%); 4/32 (12.5%) F1R 3/25 (12%); N2 CarS 0 60-d-old mice– F1S 1/39 (2.6%); 1/65 (1.5%) F1R 3/25 (12%); 2/28 (7.1%) Basal cell carcinomas: 4-d-old mice– F1S 1/39 (2.6%); 5/32 (15.6%); F1R 0; N2 CarS 5/16 (31.3%); 60-d-old mice– F1S 1/39 (2.6%); 11/65 (16.9%)[m] F1R 0; 0	[m]$P < 0.03$ vs unirradiated F1S or irrariated F1R mice
Mouse, *Ptch1* $^{neo67/+}$ (M, F) Lifespan Mancuso *et al.* (2006)	0, 3000 mGy X-rays at anagen or telogen hair growth phase 60 and 54 anagen, 56 telogen, 27 controls	Basal cell carcinomas (%): A1[1]–87.2 A2[2]–78.4 Telogen–57.5	A1 vs T2[3] $P = 0.0038$ A2 vs T2 $P = 0.05$
Mouse, *Ptch1* $^{neo67/+}$ (M, F) Lifespan Pazzaglia *et al.* (2006)	0, 3000 mGy X-rays mice irradiated at developmental stage Postnatal day 1 (P1) or day 10 (P10) P1: 20 +/+, 21 +/– P10: 24 +/+, 33 +/–	Medulloblastomas: Controls–2/15 (6.7%) P1–17/21 (81%) P10–1/33 (3%)	
Mouse, CD1 *Ptch1* $^{neo67/+}$ C57BL/6 *Ptch1* $^{neo67/+}$ (M, F) Lifespan Pazzaglia *et al.* (2009)	X-rays 0, 100, 250, 500 mGy whole body at Day 1 of age 3000 mGy-CD1 *Ptch1* $^{neo67/+}$ 3000 mGy -C57BL/6 *Ptch1* $^{neo67/+}$ 3000 mGy at P1, P2, P4, P10- CD1 *Ptch1* $^{neo67/+}$ 15–45; 22–51 controls	Medulloblastomas: 0, 100, 250, 500 mGy 4/51 (7.8%), 6/42 (14.3%), 12/42 (28.6%) [n], 18/36 (50%) [o] 0 or 3 Gy-CD1 *Ptch1* $^{neo67/+}$ 7.7, 81.0 0 or 3 Gy-C57BL/6 *Ptch1* $^{neo67/+}$ 40 [p], 50 3 Gy-P1, P2, P4, P10 (%) 81.0, 60, 50, 3.0	[n]$P < 0.0113$; [o]$P < 0.0001$ [p]$P < 0.001$ vs CD1Ptch1$^{+/-}$

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Number/group at start Dosing regimen	Incidence of tumours	Significance
Mouse, BALB/C *p53* –/–, +/–,,+/+ (M, F) Lifespan Mori *et al.* (2003)	0 or 4000 mGy X-rays *p53*+/–: 44 F, 19 M *p53*+/+: 31 F, 18 M 0 or 4 × 700 mGy *p53*+/–: 23 *p53*+/+: 26	Thymic lymphomas: 4000 mGy; 4 x 700 mGy *p53*+/– M–13/19 (68%); NR *p53*+/+ M–3/18 (17%); NR *p53*+/– F–26/44 (59%); 15/23 (65%) *p53*+/+ F–4/31 (13%); 0 Mammary tumours: 4000 mGy; 4x700 mGy *p53*+/– F– 15/44 (34%); 7/23 (30%) *p53*+/+ F–0; 15/23 (65%)	NR
Mouse, BALB/CxMSMF1 *p53* +/+, +/– and *Atm* +/+ and +/– (M, F) Lifespan Umesako *et al.* (2005)	0, 5000 mGy X-rays at 5 wk Number/group at start (NR)	Mammary tumours: *p53*+/+ *Atm*+/+ 0, 1/53 (2%) *p53*+/+ *Atm* +/– 0, 0 *p53*+/– *Atm* +/+ 7/22 (32%); 19/61 (31%) *p53*+/– *Atm* +/–14/28 (50%); 32/55 (58%) [q]	[q]$P = 0.0034$ vs *p53*+/– *Atm*+/+
Mouse, C57BL/6 Eμ-*pim*-1 and wild type C57BL/6 (M, F) 250 d after the last exposure van der Houven van Oordt *et al.* (1998)	Controls: 13 F, 12 M Eμ-*pim*-1 13 F, 11 M wild type 4 × 1500 mGy: 12 F, 14 M Eμ-*pim*-1 15 F, 18 M wild type 4 × 1000 mGy: 15 F, 11 M Eμ-*pim*-1 15 F, 16 M wild type 4 × 500 mGy: 32 F, 31 M Eμ-*pim*-1 25 F, 38 M wild type	(10%) 0 26/26 (100%) 19/31 (61%) 20/22 (90%) 6/31 (19%) 17/61 (28%) 0/62 (0%)	
Rat, Sprague-Dawley (F) Lifespan Dicello *et al.* (2004)	0, 500, 1600, 5000 mGy ^{137}Cs and ^{60}Co at ~60-d-old 18–36/group	Mammary tumours excess incidence (%): ^{137}Cs and ^{60}Co 12, 20	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Number/group at start Dosing regimen	Incidence of tumours	Significance
Rat, Sprague-Dawley (F) 1 yr Imaoka *et al.* (2007)	0, 500, 1000, 2000 mGy ^{137}Cs whole body at 8-wk-old	Mammary tumours: 3/45 (7%); 4/20 (20%); 6/20 (30%)[r]; 11/20 (55%) [s]	[r]$P < 0.05$ [s]$P < 0.0001$
Rat Otsuka Long-Evans Tokushima Fatty (M) 564 d Watanabe & Kamiya (2008)	X-rays–two doses of 10000 mGy with a 3-d interval (total dose 20000 mGy) at 5-wk-old Number/group at start (NR)	Insulinoma [pancreatic adenomas]: 0–6/19 (32%) 2x10000–19/30 (63%)	 $P < 0.01$
Rhesus Monkeys (M, F) Lifespan Broerse *et al.* (2000) and Hollander *et al.* (2003)	X-rays–2800–8600 mGy, average dose 7100 mGy 20, 21 controls	Malignant tumours Controls–7/21 (30%) X-rays–10/20 (50%) Mean age: Controls–28.4 yr X-rays–15.0 yr	 NR
Mouse, C57BL/6 (F) and B6C3F1 offspring (M, F) 120 wk Dasenbrock *et al.* (2005)	0; 2x2000 mGy X-rays F0: 216 M; 450 F F1: 1690 animals (M, F)	Hepatocellular carcinomas: Mothers– Controls 1/219 (0.4%) X-rays 9/230 (4%) Male offspring– Maternal 0 (16%) historical controls Maternal X-rays 53/210 (25%) Lung tumours: Mothers– Controls 7/219 (3%) X-rays 25/230 (11%) Male Offspring– Maternal 0 (27%) historical controls Maternal X-rays 82/210 (39%)	 $P < 0.05$ $P < 0.01$ $P < 0.05$

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Number/group at start Dosing regimen	Incidence of tumours	Significance
Mouse, B6C3F1 (F) 550 d Sasaki & Fukuda (2008)	^{137}Cs γ-rays doses from 100 to 5700 mGy at 17 day prenatal and Days 0, 7, 35, 105, 240, 365, 550 of age	ERR at 1000 mGy Ovarian tumours: 17 day prenatal 1.43 ± 0.21 Day 0–15.8 ± 1.5 Day 7–29.2 ± 5.0 Day 35–21.7 ± 6.0 Day 105–10.9 ± 1.1 Day 240–1.54 ± 0.04 Day 365–1.23 ± 0.20 Day 550–1.26 ± 0.06	

d, day or days; ERR, excess relative risk; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; PC, post conception; TPA, 12-*O*-tetradecanoylphorbol-13 acetate; vs, versus; wk, week or weeks; yr, year or years

[1] A1; Anagen 1, mouse dorsal skin at postnatal day 3 (P3)

[2] A2; Anagen 2, mouse dorsal skin at postnatal day 35 (P35)

[3] T2; Telogen 2, mouse dorsal skin at postnatal day 60 (P60)

soft-tissue sarcomas and haemangiosarcomas in both sexes, and an increase in myeloid leukaemia in males and malignant granulosa cell tumours in females. An increase in multiple primary tumours was seen in both male and female mice at the dose of 21 mGy per day (8000 mGy total dose) but not at the lower doses and dose rates.

Pazzaglia *et al.* (2002a) used the CAR-S and CAR-R mice (10–12 weeks of age) that had been selected based on genetic susceptibility to skin-tumour induction by chemical carcinogens to examine the genetic control of skin tumorigenesis following X-ray initiation and TPA (12-*O*-tetradecanoylphorbol-13-acetate). These studies used four weekly fractions of 1500, 2000 and 2500 mGy followed by TPA. An increase in frequency of tumours and shortening of latency was observed in all groups in CAR-S (carcinogenesis sensitive) mice, while no effect was seen in CAR-R (carcinogenesis resistant) mice, which were selectively bred based on sensitivity to chemical carcinogens.

3.3.2 Transgenic mice

Several recent studies have used genetically engineered mice to examine effects of X-rays and γ-rays on tumorigenesis. Most studies focused on effects in either Apc^{Min+} mice (Min mice) that contain a nonsense mutation in the *Apc* gene at codon 850 resulting in a truncated protein, as well as Apc1638N mice or $Ptch1^{\pm}$ mice containing only one allele of the *Patched1* gene. The Apc^{Min} mutation is the mouse homologue of human familial adenomatous polyposis. This heterozygous mutation predisposes mice to the spontaneous development of small intestine tumours and to radiation-induced tumorigenesis in both the small intestine and mammary gland. Apc1638N mice display a relatively more mild phenotype with respect to multiplicity in non-treated controls. In all instances, the tumours that arise involve the loss of the wild-type allele. *Ptch1* mice are analogous to individuals with Gorlin Syndrome who inherit a germ-cell mutation in *Ptch*. These individuals and their murine counterparts have an increased incidence of basal cell carcinoma and medulloblastoma. These mice and humans are also hypersensitive to radiation-induced tumours in terms of both basal cell carcinoma and medulloblastoma. As in the case of *Apc*, loss of the wild-type *Ptch* allele has been shown to be involved in radiation-induced tumorigenesis.

Okamoto & Yonekawa (2005) reported on the induction of intestinal tumours as a function of X-ray dose and age at exposure in Apc^{Min+} mice. Doses used were 250, 500, 1000 and 2000 mGy at ages of 2, 10, 24, 42, and 48 days of age. Doses of 1000 and 2000 mGy resulted in a significant increase in the multiplicity of tumours of the small intestine in all age groups with a peak at 10 days of age. Using 10-day-old mice, these investigators reported a proportional increase in multiplicity at all doses used. For colon tumours, no increase was seen at doses of 250 and 500 mGy while significant increases were observed at 1000 and 2000 mGy. The peak in sensitivity as a function of age shifted slightly with peak sensitivity at 2 days of age. Irradiation at 24 days or later resulted in no significant increase in colon tumours.

Imaoka *et al.* (2006) examined the age dependency of mammary tumours in Min mice following a dose of 2000 mGy at 2, 5, 7, and 10 weeks of age. While the number of animals in each group was small, mice irradiated at 7 and 10 weeks of age were found to have a significant increase in the frequency of adenoacanthomas, while mice irradiated at 2 and 5 weeks of age did not. Rather, these mice developed cystic nodules with metaplasia.

Degg *et al.* (2003) examined adenoma multiplicity in the small intestine of Min mice on the BALB/c background after a dose of 2000 mGy, and linked sensitivity to a segment of chromosome 16 containing a variant form of *Prkdc*, the gene encoding DNA-dependent protein kinase.

A later study from the same laboratory (Ellender *et al.*, 2005) found that direct single gene mutational events in the *Apc* gene could account for increased frequencies of intestinal tumours after doses of 2000 and 5000 mGy. Further, this laboratory (Ellender *et al.*, 2006) reported on *in utero* and neonatal sensitivity to increased frequency of intestinal tumours. The data for 2-, 10- and 35-day-old animals were similar to that of Okamoto & Yonekawa (2005), with peak sensitivity at 10 days of age. No increase in the frequency of tumours was observed in mice irradiated *in utero* at 7 or 14 days post conception (Okamoto & Yonekawa, 2005).

The studies above focused on all intestinal tumours but mainly adenoma, Nakayama *et al.* (2007) reported a significant increase in the frequency and multiplicity of invasive carcinoma in the small intestine in the Apc^{Min+} mice following a single dose of X-rays of 5000 mGy. An increased frequency of mammary tumours was also seen but no increase in colon tumours was observed.

Using the Apc1638N mouse model, van der Houven van Oordt *et al.* (1997) first demonstrated their sensitivity to intestinal and mammary tumorigenesis. Sensitivity to the induction of both intestinal tumours and mammary tumours was later shown to be dependent on the genetic background of the mice after a 5000 mGy dose of X-rays. In one study, background sensitivity to the induction of ovarian tumours was also observed (van der Houven van Oordt *et al.*, 1999).

Pazzaglia *et al.* (2002b) first reported a significantly increased frequency of medulloblastoma following 3000 mGy of X-radiation in *Ptch1* heterozygous mice irradiated at 4 days of age. Subsequently, significantly increased frequencies of basal cell carcinoma were reported following doses of 3 and 4 Gy in *Ptch1*-deficient mice by the same investigators (Mancuso *et al.*, 2004). It was also demonstrated that susceptibility to basal cell carcinoma could be modified by genetic background (Pazzaglia *et al.*, 2004). Hair cycle phase was also shown to be important in the carcinogenic effect of radiation (Mancuso *et al.*, 2006). During growth phases in the hair cycle, both a quantitative increase in frequency of tumours and a qualitative effect on tumour type were observed. The stage of development was also shown to be an important factor that linked sensitivity to DNA damage and apoptosis (Pazzaglia *et al.*, 2006).

A following study examined the dose response for the induction of medulloblastoma in the *Ptch1*-knockout mice after X-ray doses of 100, 250, and 500 mGy (Pazzaglia *et al.*, 2009). A significantly increased frequency of these tumours and concomitant decrease in survival time was observed in mice irradiated at doses of 250 and 500 mGy, with a linear dose–response relationship adequately describing the entire data set. Sensitivity to induction was age-dependent with a decrease in sensitivity with increasing age over the 1–10-day age time period following a 3000 mGy dose of X-rays.. This sensitivity was correlated to a resistance to apoptosis in cells from younger mice (Pazzaglia *et al.*, 2006, 2009). These investigators also published evidence for the participation of bystander effects in the induction of medulloblastoma following 3000 mGy of X-radiation (Mancuso *et al.*, 2008).

Mammary tumorigenesis has been studied in BALB/c $p53^{+/-}$ mice. Mori *et al.* (2003) compared effects following a 4000 mGy dose delivered as a single dose versus weekly fractions. With both single dose and fractionated doses, $p53^{+/-}$ mice were significantly more sensitive to tumour induction following irradiation. After a single dose, lymphomas were the primary cause of death although an increase in mammary tumours and sarcomas were observed. Following fractionation, mammary carcinomas were dominant with these tumours showing a frequent loss of the *p53* wild-type allele (Mori *et al.*, 2003). Umesako *et al.* (2005) subsequently demonstrated that ataxia-telangiectasia mutated (*Atm*) heterozygosity enhanced the development of mammary

tumours in BALB/c *p53*$^{+/-}$ mice after 5000 mGy of X-rays. Loss of the wild-type *p53* allele but not *Atm* was found in these tumours.

Studies of Eμ-*pim*-1 transgenic mice following four weekly fractions of 500, 1000, or 1500 mGy were reported by van der Houven van Oordt *et al.* (1998). An increased frequency of lymphomas was observed at all total doses with the highest effect observed in the 4 × 1000 mGy group, with 91% of the mice developing lymphomas. In this model, molecular events appear to involve alterations in *myc* expression.

3.3.3 Rat

Two studies in rats focused on the induction of mammary carcinoma in adult rats. In the first study, Dicello *et al.* (2004) examined the effect of ^{137}Cs and ^{60}Co γ-rays in Sprague-Dawley rats as part of a study that focused on comparing effects of γ-rays with 250 MeV protons and 1 GeV/nucleon ^{56}Fe ions. Dose of γ-rays used were 500, 1600, and 5000 mGy. A significant increase in frequency of mammary tumours was observed at doses of 1600 and 5000 mGy, and a slight but not statistically significant decrease was found at a dose of 500 mGy. In spite of the slight decrease at 500 mGy, a linear dose–response relationship was the best fit for the data.

In the second study, Imaoka *et al.* (2007) examined rat mammary induction following ^{137}Cs irradiation as part of a study comparing 290 MeV/nucleon carbon ions in Sprague-Dawley rats at doses of 500, 1000 and 2000 mGy. A significant increased frequency and multiplicity of carcinomas was observed at all three doses with an apparent linear dose–response relationship.

Bartel-Friedrich *et al.* (1999) reported a significant increase in malignant tumours of the head and neck (squamous cell carcinoma and adenoid cystic carcinoma in the irradiated field) in the Wistar strain of rats following partial body irradiation at 2000 mGy per day fractionated exposures of X-radiation to a total dose of 60000 mGy.

Watanabe & Kamiya (2008) reported a significant increase in insulinomas [islet cell adenomas] in Otsuka Long-Evans Tokushima Fatty rats following two doses of 10000 mGy separated by 3 days (20000 mGy total dose) of X-rays to the gastric region. No tumours were seen in controls, but 19/30 rats (63.3%) developed insulinomas following irradiation.

3.3.4 Rhesus monkey

Two reports of studies on tumorigenesis in monkeys following exposure to radiation have been published on the same cohort (Broerse *et al.*, 2000; Hollander *et al.*, 2003). Both publications reported the tumour frequencies of X-irradiated monkey that were approximately 3 years of age at the time of irradiation. The 20 animals received doses ranging from 2800–8600 mGy with an average dose of 7100 mGy. An increased frequency (50%) and decreased latent period (12 years) of malignant tumours were observed when compared to 21 controls (30% and 28.4 years respectively). The tumours seen were very diverse. A specific increase in kidney cortical carcinoma (with none being found in controls) was observed (38%; 8/21). An increase in benign tumours was also found.

3.4 Prenatal exposure

After prenatal exposure of mice to ^{137}Cs γ-rays, Sasaki & Fukuda (2008) compared ovarian tumorigenesis as a function of age from 17 days post conception through 550 days of age. This study suggests that sensitivity to prenatal radiation exposure is determined by the developmental stage of the organ system, which impacts the number and proliferative activity of target cells.

3.5 Neonatal exposure

The characteristics of life-shortening and carcinogenesis were investigated in neonatal $B6WF_1$ mice irradiated with X-rays. Animals were irradiated within 24 hours after birth with 0 (control), 200, 400, or 600 R [an exposure to 1R is approximately equivalent to 10 mGy] of X-rays, and allowed to complete their normal lifespan (n = 532) or observed until 500 days old (n = 35 males). Mean lifespan was shortened linearly with dose at a rate of 9.1% per 100 R for females and 9.8% for males. The spectrum of neoplastic diseases was apparently modulated by irradiation with X-rays, showing neonatal $B6WF_1$ mice to be highly susceptible to the induction of thymic lymphoma (tumour incidence: 1%, 2%, 14% ($P < 0.05$), and 48% ($P < 0.05$), in females; 0%, 5%, 13% ($P < 0.05$), and 43% ($P < 0.05$), in males; respectively, for increasing doses), liver carcinoma (tumour incidence: 0%, 6% ($P < 0.05$), 16% ($P < 0.05$), and 12% ($P < 0.05$), in females; 0%, 12% ($P < 0.05$), 36% ($P < 0.05$), and 14% ($P < 0.05$), in males; respectively, for increasing doses), and pituitary tumour [tumour type not specified] (tumour incidence: 5%, 14% ($P < 0.05$), 24% ($P < 0.05$), and 12% ($P < 0.05$), in females; respectively, for increasing doses). The dose–response relationship for thymic lymphoma could be described by a linear–quadratic model, and linearity could be rejected. Thymic lymphoma developed after a short latent period, resulting in death between 100 and 450 days of age. Liver and pituitary tumours increased with increasing dose up to 400 R and decreased thereafter. The latent period for liver tumour development was apparently shortened with increasing doses. Pituitary tumours developed in excess only in females after a long latent period. An increase in the incidence of ovarian tumours [tumour severity not specified] (1%, 10% ($P < 0.05$), 12% ($P < 0.05$), and 4%; respectively, for increasing doses), of Harderian gland tumours [tumour severity not specified] (1%, 6%, 8% ($P < 0.05$), and 3%; respectively, for increasing doses), and of vascular tumours (haemangioma and haemangiosarcoma combined; 9%, 16%, 24% ($P < 0.05$), 1%; respectively, for increasing doses) was aslo observed in female mice (Sasaki & Kasuga, 1981).

3.6 Parental exposure

Only one report of parental exposure has been published (Dasenbrock *et al.*, 2005). In this study, female C57BL6/6N mice received two 2000 mGy doses separated by 2 weeks (4000 mGy total dose) before mating with non-irradiated C3H/HeN males. After weaning, half the offspring were exposed to ciclosporin, with the other half remaining untreated and maintained for their lifespan. Significant increases in lung adenoma and hepatocellular carcinoma were observed in the irradiated females. A significantly increased incidence of benign and malignant lung tumours combined and hepatocellular carcinoma was found in the non-irradiated male progeny of irradiated mothers (Table 3.1).

3.7 Synthesis

Studies conducted since the year 2000 have provided new information on radiation-induced cancer that includes dose–response relationships for tumour induction. Significantly increased frequency of tumours and/or tumour multiplicity were observed in mice, rats, and monkeys. Often, the use of X- or γ-rays was mainly for the purpose of comparing other types of radiations to measure differences in effectiveness. The studies focusing directly on the effects of X- and γ-rays were designed either to address effects at low doses or to use transgenic or genetically sensitive or resistant mice mainly to address potential mechanisms of action or genetic control of sensitivity. In the case of *Ptch1* mice, this very sensitive model was also exploited to examine cancer risk as a function of dose. All of the data

in all species examined confirmed that exposure to X- and γ-rays can increase the risk for tumour induction. It is important to emphasize that risks can be modified substantially by dose and dose rate, age at exposure, and genetic background. Studies in Apc^{min+} and *Ptch1* mice also provided information suggesting that stem cells or early progenitor cells are a likely target for these carcinogenic effects, and/or variance in sensitivity as a function of age.

X-rays and γ-rays cause malignant lymphoma (including thymic lymphoma), myeloid leukaemia, malignant mammary tumours, ovary cancer, liver cancer, intestine (small) and colon tumours, haemangiosarcoma and skin basal cell carcinoma in mice; malignant mammary tumours and thyroid cancer in rats. X-rays cause a variety of malignant tumours including kidney cortical carcinomas in monkeys.

4. Other Relevant Data

4.1 Radionuclides: determining the distribution of dose

Most radionuclides are in themselves not toxic—uranium is a notable exception. This is because during their period of existence within the body, they are rarely present in sufficient mass to exhibit any chemical toxicity. It is only when they cease to exist and their decay is accompanied by the release of radiation that toxic effects may be produced. With respect to toxicity, the most important of the radiations produced by radionuclide decay are α-particles and β-particles (positrons and negatrons), but other emissions such as fission fragments may also be important (e.g. for ^{252}Cf). It follows that the characteristics of the radionuclides in the cytotoxic and carcinogenic processes determine the eventual distribution of the emitted radiations within the cells and tissues of the body.

Occupational and environmental intakes of radionuclides result from exposures to either radionuclides within aerosols by inhalation (Khokhryakov *et al.*, 2000; Gilbert *et al.*, 2004), radionuclides present in food and water by ingestion (Ham *et al.*, 1994; Hunt, 1998), radionuclides deposited on the skin by skin absorption or by puncture wounds that result in the transfer of radionuclides from contaminated surfaces. These processes are often independent of the physicochemical form of the radionuclide, but do depend upon factors such as the age of the subject and the size of the radionuclide uptake. For example, radionuclide uptake from the gut is higher in infants than in adults (Bomford & Harrison, 1986), the mass of radionuclide in the gut can influence uptake, and the deposition and retention of radionuclides in the lung depends upon both the mass inhaled and the size of the lungs and their airways (ICRP, 1995). All subsequent behaviour of radionuclides in the body is a function of their ability to dissolve/disperse within tissue fluids, and a function of their chemical affinity to body components (Priest, 1990). Unabsorbed radionuclides present either on the skin or in the lungs and gastrointestinal tract irradiate local cells and tissues, and tumours may result. For example, there is a wide body of evidence demonstrating the carcinogenicity of inhaled radionuclides in man (e.g. Gilbert *et al.*, 2004).

Following transfer from their site of initial deposition, most radionuclides enter the bloodstream where they remain until they either deposit in organs and tissues or are excreted in urine, faeces and, less commonly, in sweat, hair, skin, and nails. Most elements are polyvalent metals and these tend to interact with the metabolic pathways that exist in the body for essential metals—most importantly calcium and iron. The radionuclides of these elements, therefore, tend to deposit at sites of calcium and iron deposition and storage within the body – including, but not exclusively, within the skeleton – and are

commonly referred to as bone-seeking radionuclides. Other monovalent metals and non-metals do not interact with the metabolic pathways for calcium and iron and are either deposited specifically at other sites (e.g. iodine in the thyroid gland) or become widely distributed throughout (e.g. potassium and caesium) and/or incorporated in all body tissues (e.g. hydrogen, carbon, sulfur, and phosphorus). It follows that for ease of description, radionuclides can be categorized as either bone-seeking or as non-bone-seeking.

4.1.1 Internal dose assessment

As mentioned in Section 1.2, radionuclides can enter the body by inhalation, ingestion, absorption or injection/wound, this is known as an internal exposure. The threshold of detection for direct measurement ('Whole Body Monitoring') of some internal α- or β-particles emitters *in vivo* can be many times greater than the recommended annual dose limits, and others are essentially undetectable *in vivo*. Hence, individuals' doses from internal exposures are commonly "assessed" indirectly using mathematical models that describe radionuclide absorption, distribution, metabolism and excretion (ADME). The ICRP are the principal source of information on this topic, and their current recommended models of radionuclide ADME and dosimetry can be found in their recent publications.

It should be noted that internal dose assessment is still an incomplete science, and there are several issues that should be considered when evaluating the results of epidemiological studies involving internally deposited radionuclides. The methodology employed to calculate internal doses has continued to improve, over time, as knowledge of radionuclide ADME has improved (much of the evolution of models of radionuclide ADME can be seen by reviewing the previous publications of the ICRP). A primary route of absorption of many internally deposited radionuclides is through inhalation. Modelling the transport of radionuclides from the lung to the blood with true fidelity remains a key issue as this can have a substantial impact on assessed doses (Riddell, 2002). Internal dose assessments often also rely on radionuclide measurements either in the environment (e.g. air concentration) or bioassay samples (e.g. urinalysis). The resolution and reliability of radionuclide measurement techniques have also shown significant improvements over time. To a certain extent, the internal dose assessment process still requires some measure of expert judgement. Consequently, the dose estimates produced for one epidemiological study may not be comparable, in terms of both accuracy and precision, with those from another. Furthermore, the uncertainties associated with internal dose estimates, particularly for the lung following the inhalation of radionuclides, are generally significantly greater than those associated with external radiation exposures. Finally, the assessment of doses from radionuclides released into the environment may also be based on mathematical models of environmental transport of these radionuclides. Because different environmental transport models may be used for studies and because of the complexity of the processes being modelled, these models may not give consistent and/or unbiased estimates of individual exposures. These considerations are important because, all other things being equal, the accuracy and reliability of the risk estimates produced by epidemiological research is directly correlated to that of the dosimetry data.

Internal exposures can be to naturally occurring or man-made radionuclides made available through natural, industrial, medical, accidental or military, processes. Information on ADME, relevant routes of internal exposure, and monitoring techniques for the radionuclides under review are considered below (this information was compiled using the sources used for Section 1.2.6, above, with the further additions of ICRP publications 54 and 78; ICRP, 1988,

1997). The information is provided to give some understanding of the key processes involved, the organs/tissues exposed, and the potential difficulties in providing unbiased estimates of exposure. For the purposes of brevity and clarity some simplifications have been made, and this should not be taken as a definitive statement on the extent of current knowledge.

(a) Tritium

The ADME of ^{3}H is fundamentally linked to that of natural body water. The majority of ^{3}H enters the body as tritiated water and in this form, whether ingested or inhaled, is totally absorbed. Significant amounts can also be absorbed through the skin. Upon entering the body, tritiated water rapidly becomes homogeneously distributed in the whole-body water content (including urine), and is cleared with the same biological half-life, 10 days, as other body water. ^{3}H can also become attached to organic compounds that are retained in the body with a longer biological half-life, ICRP suggest 40 days (ICRP, 1997), although the extent, biological half-life and significance of this organically bound fraction presently remains the subject of some debate (HPA, 2007). As ^{3}H only emits low energy β-particles, in-vivo monitoring is not feasible; individual dose assessments are normally based on urine monitoring or environmental transport models.

(b) Phosphorus-32

Knowledge of ^{32}P ADME is limited but as it is mostly used for medical purposes, initial dosages (in terms of uptake of activity) are usually quite well defined. Following injection, ^{32}P mainly accumulates in bone (~30%), where it is eliminated by radioactive decay, and is cleared from the body, primarily by urinary excretion, with a biological half-life of ~39 days (Spiers *et al.*, 1976).

(c) Strontium-90

^{90}Sr behaves similarly to natural calcium when taken into the body, although it is not retained for as long, and tends to deposit on the bone surfaces. The majority of ^{90}Sr (> 50%) is rapidly cleared from the body within a week following exposure, only a small amount remains after a year, largely in the skeleton. Approximately 30% of ingested ^{90}Sr will be absorbed into blood from the gut in adults, but this percentage can be even higher for infants; this makes ingestion an important exposure route, particularly when ^{90}Sr is released into the environment (ICRP, 1993). As ^{90}Sr is a pure β-particle emitter, urine monitoring is the preferred method of assessing individual exposures (ICRP, 1997). However, when exposure is to a known mixture of fission products, in-vivo monitoring of other fission products, such as ^{137}Cs, may be used to estimate ^{90}Sr exposure.

(d) Iodine

As with stable iodine, ^{131}I tends to accumulate in the thyroid gland. Approximately 30% of ^{131}I entering the blood will go to the thyroid, the remainder being quickly excreted from the body in urine. Retention of ^{131}I in the thyroid is age-dependent with a biological half-life in the range of approximately 11 days for infants to 80 days for adults (ICRP, 1979, 1989). Exposure to ^{131}I can effectively be blocked by loading the thyroid with stable iodine, usually through the use of iodine tablets. All ingested iodine-131 will pass from the gut into the blood. The threshold for measuring ^{131}I directly *in vivo* is three to four orders of magnitude below current recommended limits on intake, and this is the preferred method of monitoring exposure. The main consideration when calibrating is the absorption in the tissues overlaying the thyroid in the neck. If stable iodine has been used as a blocking agent, urine monitoring will be required to assess individual exposure (ICRP, 1997).

(e) Caesium-137

After being taken into the body ^{137}Cs behaves in a similar manner to naturally occurring potassium, and is fairly uniformly distributed throughout the body, with the largest deposition being in muscle, reflecting the muscle's percentage of overall body mass. Like potassium, ^{137}Cs is quickly cleared from the body; 10% with a biological half-life of 2 days, the remainder with a biological half-life of 110 days. Following ingestion, ^{137}Cs exhibits almost complete uptake to blood from the gut, therefore, this is an important exposure route particularly for ^{137}Cs in the environment. Because its radioactive daughter, metastable barium-137m, is a gamma emitter with a short radioactive half-life, 2.5 minutes, ^{137}Cs dose can easily be assessed from in-vivo measurements, although urine monitoring may also be used for this purpose (ICRP, 1997).

(f) Radon

Because ^{222}Rn is a gas and its most radiologically significant radioactive daughters have short half-lives, most of the dose from ^{222}Rn is to the lung. Air monitoring is the preferred method of assessing ^{222}Rn exposures. It is relatively easy to measure the time integrated ^{222}Rn concentration at a specific location, using for example air samplers or CR-39 plastic-based measurement devices. However, it is often difficult to accurately relate measured ^{222}Rn concentrations to individual exposures due to issues such as variability of occupancy, airflow, attached fraction, breathing rate and so forth (BEIR IV, 1988).

(g) Radium

Radium exhibits similar metabolic behaviour to calcium, and consequently a large proportion of radium that enters the blood is deposited in the skeleton and teeth. The amount in bone decreases following cessation of exposure, typically by more than 90% over a few months and 99% over a few years. Most of the radium taken into the body by ingestion (about 80%) will rapidly be excreted in faeces with only ~20% passing from the gut into blood, but historically this has been an important mode of exposure (ICRP, 1993). Direct measurement of pure ^{226}Ra and ^{228}Ra *in vivo* would not be feasible due to their low penetration primary emissions; however, daughter nuclides in both of their decay chains (e.g. lead-214 and bismuth-214 for ^{226}Ra, and actinium-228 for ^{228}Ra) are detectable *in vivo*. The presence of these decay chains, which can be in different states of equilibrium following the chemical processing of radium, can also make dosimetry complex. Urine monitoring can also be used for assessing radium doses (ICRP, 1997).

(h) Thorium-232

When ^{232}Th enters the blood, ~70% deposits in bone, primarily on the endosteal surfaces, then it is slowly redistributed throughout the bone volume, where it is retained with a biological half-life of about 22 years. Of the remaining ~30% of ^{232}Th entering blood, ~10% is rapidly excreted and ~20% deposits in the liver (~4%) and other organs/tissues (~16%), where it is retained with a biological half-life of 700 days (ICRP, 1995). The majority of ^{232}Th that is ingested is rapidly excreted, and only about 0.02 to 0.05% is absorbed into the blood from the gut, but this is still the primary route of exposure in the general population from ^{232}Th in the environment. Inhalation is an important exposure pathway for occupational exposures (e.g. miners). Direct measurement of pure ^{232}Th *in vivo* would not be feasible due to the low penetration of its primary emission, however, a daughter nuclide, ^{228}Ac, in its decay chain is detectable *in vivo*. The presence of this decay chain, which can be in different states of equilibrium following the chemical processing of ^{232}Th, can also make dosimetry complex. Faecal and urine measurements can also be used for ^{232}Th monitoring (ICRP, 1997).

(i) Uranium

Uranium entering the blood is mainly (~22%) deposited in the bone volume, where it is retained long-term, and kidneys (~12%), with the remainder either being distributed throughout the body (~12%) or rapidly excreted. Only a small fraction (~0.2% to ~2%) of ingested uranium is absorbed from the gut into the blood, but this is still the main source of exposure for uranium in the environment (ICRP, 1995, 1997). Inhalation is an important pathway for occupational exposures but there is considerable debate and uncertainty in relation to the rate at which uranium compounds pass from the lung to the blood, and this can make substantial (up to orders of magnitude) differences in the calculated lung doses (Riddell, 2002). Air sampling, urine and in-vivo measurements are all used for the individual monitoring of uranium depending on the exposure scenario. In-vivo monitoring is reliant on the detection of gamma emissions from ^{235}U, obviously this is easier with highly enriched uranium but it is possible, with poorer sensitivity, with lower levels of ^{235}U within the isotopic mix. It should be noted that the limit on occupational exposure for uranium, for common forms that are fairly readily absorbed into blood from the lung (default types 'F' (fast absorption) and 'M' (moderate absorption)) (ICRP, 1994), is commonly based on chemical toxicity in the kidney and not on the radiation dose (ICRP, 1997). It should also be noted that in certain locations, individuals could have significant levels of uranium in their urine as a result of their dietary intake of naturally occurring uranium. Conversely, in other locations, excretion due to dietary intake may be significantly lower than reference levels (Riddell, 1995).

(j) Plutonium

Plutonium is retained long-term by the body once it enters the blood mainly in the liver and skeleton, where it is deposited on the cortical and trabecular surfaces of bones, and is slowly redistributed throughout the bone volume over time, with a biological half-life of the order of decades. Most exposure to plutonium has been in the occupational setting, i.e. those involved in nuclear weapons or nuclear power production, and the primary exposure pathways are inhalation and, to a much lesser extent, wounds. Considering that inhalation is the most important exposure pathway, there is still considerable debate and uncertainty in relation to the behaviour of plutonium in the lung, and this can make a substantial difference to the calculated lung doses (Harrison, 2009). Only a small percentage (~0.001% to ~0.05%) of plutonium that enters the gut is absorbed into blood, and consequently ingestion is not usually a major exposure pathway. Urine and faecal sampling, in-vivo measurements and air sampling have all been used for plutonium monitoring. Because urine is relatively easy to collect, urinalysis results are the basis of most of the assessed internal plutonium doses. The quality, in terms of resolution and freedom from adventitious contamination, and quantity of urine sample data has a fundamental impact on the accuracy and reliability of dose assessments. Urine samples collected from workers historically are known to suffer from adventitious contamination, and the analysis techniques used had poor resolution (Riddell *et al.*, 2000). In-vivo measurements suffer from poor sensitivity, the threshold of detection often equates to a dose that is several times greater than recommended annual dose limits but may be the only option for very insoluble compounds in the lung (ICRP, 1997). As reprocessing has increasingly turned towards spent nuclear fuel from civil power reactors, ^{241}Pu and its radiologically significant daughter ^{241}Am have been seen in greater quantities. In such cases, measurements of ^{241}Am ingrown from ^{241}Pu can be used for assessing exposures from known plutonium isotope mixtures (ICRP, 1997).

4.1.2 Bone-seeking radionuclides

Bone-seeking radionuclides are so-called because of their tendency to be deposited in, and be retained by, bones and teeth. This group of radionuclides includes most of those that are either commercially important and/or are widely recognized to be important potential human carcinogens, including alkaline earth radionuclides (e.g. ^{45}Ca, ^{90}Sr, and ^{226}Ra), transition element radionuclides (e.g. ^{90}Y, ^{55}Fe, and ^{65}Zn) and the lanthanon (lanthanide) and actinon (actinide) radionuclides (^{147}Pm, ^{234}U, ^{239}Pu, ^{241}Am, and ^{244}Cm). Many reviews of the deposition, retention and toxicity of plutonium and other bone-seeking radionuclides have been published (AEC, 1971; Durbin, 1973; Vaughan *et al.*, 1973; AEC, 1974; ICRP, 1986; BEIR IV, 1988; Priest, 1990).

There are of two main types of bone seeker:

1) those that are chemically related to normal bone components—examples that are known to produce cancer in either man or animals include ^{32}P, ^{90}Sr, ^{133}Ba, ^{65}Zn, ^{226}Ra, and ^{235}U;

2) those that are chemically unrelated to normal bone components but bind to the mineral and matrix components of bone—examples include ^{90}Y, ^{55}Fe and radionuclides of most transition metals, lanthanons (lanthanides), and actinons (actinides).

When present in the skeleton, all have the potential to irradiate radiation-sensitive cells – mostly within the bone-marrow cavity – to produce a variety of skeletal tumours including fibrosarcoma, chondrosarcoma, osteosarcoma, multiple myeloma, and leukaemias (Durbin, 1973; Koshurnikova *et al.*, 2000; Shilnikova *et al.*, 2003). In addition, many of the bone-seeking radionuclides are present in a wide variety of other tissues resulting in extra-skeletal tumours, such as hepatic carcinoma (Gilbert *et al.*, 2000). In general, radionuclides that become extensively deposited within the volume of the bone matrix (bone-volume seekers) are less toxic than those that mostly remain close to bone surfaces (bone-surface seekers) (Taylor *et al.*, 1983). However, this distinction is not clear, and in practice many radionuclides are present in both bone volume and surface components. For example, all bone-volume seekers transit through bone surfaces before deposition, and the apposition of new bone onto contaminated surfaces buries bone-surface seekers. The lower toxicity of buried radionuclides results from the high fraction of the α- and β-particles released by these that are harmlessly attenuated by the bone mineral. In contrast, bone-surface seekers are deposited and commonly retained adjacent to the radiation-sensitive cancer precursor cells found within the marrow space close to bone surfaces, and deeper within the bone marrow (Priest, 1990).

In addition to the above, radioactive colloids have sometimes been used either for radiotherapy or as a radiographic contrast agent, and these are carcinogenic. Of these, the most important is Thorotrast, a colloidal suspension of thorium (^{232}Th) dioxide, which was used from the 1930s through to the 1950s. This was mostly injected into patients as a radiographic contrast agent, but following its injection and clearance from the blood, it became deposited within the reticulo-endothelial system – mostly in the liver, spleen, and red bone marrow. Subsequently, up to 40% of the patients injected with Thorotrast, who had survived the trauma that indicated the use of the agent, developed either malignancies or liver cirrhosis, and died as a result of irradiation by ^{232}Th and its progeny (Becker *et al.*, 2008). Most of the tumours produced were hepatic carcinomas, but myeloid leukaemia was also common. While not a bone-seeking radionuclide, the sites of Thorotrast deposition in the body are sufficiently close to those of many bone-seeking radionuclides to inform on the toxicity of the latter.

(a) Radionuclides chemically related to normal bone components

Classically, the most important of the radionuclides that are chemically related to normal bone components are the alkaline earth elements (beryllium, calcium, strontium, barium, and radium), the uranyl ion (UO_2^{2+}), and those that may form anions similar to phosphate (PO_4^{2-}). This includes several important radionuclides including ^{32}P, ^{90}Sr, ^{133}Ba, ^{224}Ra, ^{226}Ra, ^{233}U, and ^{234}U for which extensive animal and human toxicity data exists. All of these are deposited within bone mineral (calcium hydroxyapatite), but several mechanisms for their incorporation are possible (Priest, 1990). Following their introduction into the body, all tend to be present in blood and tissue as freely exchangeable divalent ions associated with low-molecular weight plasma components such as bicarbonate. Their uptake and retention by tissues other than the skeleton is low, consequently most of those that are not deposited within the skeleton are rapidly excreted in either the urine or faeces—where due to short-term retention they may cause kidney damage, e.g. kidney damage by uranium. [The Working Group noted that this recent evidence suggests significant uptake of radium isotopes by the thyroid gland at levels of concentration similar to those in bone, and these may contribute to the induction of thyroid cancer. Also, if such deposits are confirmed for other alkaline earth radionuclides, such as ^{90}Sr, they also may, in part, explain the excess thyroid cancer seen in irradiated populations following the Chernobyl nuclear accident.]

Uranium is a special case and is worthy of further consideration (The Royal Society, 2001, 2002). Six isotopes are important: ^{232}U and ^{233}U are anthropogenic and produced in thorium-fuelled reactors; ^{236}U is produced in reactors by neutron capture; and ^{234}U, ^{235}U and ^{238}U are naturally occurring isotopes. The half-life of these varies greatly and that of ^{238}U is so long (4.47×10^9 yr) that it is minimally radioactive. It is therefore not axiomatic that any mutagenic effects of ^{238}U (including both natural uranium and depleted uranium) will have been produced by tissue irradiation. Indeed, there is evidence that low specific activity forms of uranium may exert their effects as a manifestation of its chemical toxicity. In contrast, high specific activity isotopes – ^{232}U and ^{233}U – are most unlikely to be present in the body in sufficient quantities to produce significant chemical toxicity, and radiation effects will dominate. In addition, uranium exists in two almost similarly stable valence states: U^{4+} and U^{6+}. There is some evidence the tetravalent form behaves like other actinons; however, in biological systems hexavalent uranium (as UO_2^{2+}) is most important. Due to the bivalency of this complex ion, it shares many characteristics in common with the alkaline earth elements that also exist in the form M^{2+}. These are all bone-seeking radionuclides that deposit in the skeleton with a pattern similar to that of calcium.

In the adult skeleton, most bone surfaces are inactive at any one time and in adult man only about 22% of trabecular bone and 3% of cortical bone surfaces are remodelled (removed and re-deposited) in any year—in children, the fraction is much higher and age-dependent. It follows that in adults, the bulk of alkaline earth radionuclides and the uranyl ion radionuclides initially transfer from tissue fluids to quiescent bone surfaces where they deposit as a close-to-infinitely thin layer (Priest, 1990). The most likely explanation for this is their uptake by ion-exchange processes either into existing bone mineral crystals or within the hydration shell that surrounds each bone crystal. On growing bone surfaces, the density of uptake is higher and the radionuclides become deposited at the bone-mineral face below the layer of un-mineralized bone matrix referred to as osteoid. At these sites, it is postulated that the radionuclide is incorporated into the forming bone crystals. Subsequently, autoradiographic studies have shown that most of the

radionuclide on the quiescent bone surfaces is lost to back-exchange, leaving radionuclide hotspots at sites of bone deposition. These then become buried as new bone is deposited, and over time successive bone turnover cycles result in a more uniform deposition of radionuclide throughout the bone volume—hence the term bone-volume seeker. It follows that the fraction of radionuclide that decays close to bone surfaces will be a function of the half-life of the radionuclide. Short-lived radionuclides such as ^{224}Ra (half-life, 3.6 days) will decay close to bone surfaces and be more toxic per unit of average skeletal dose than long-lived radionuclides emitting the same radiation type such as ^{226}Ra and ^{234}U. This is both because of the higher fraction of radionuclide that decays near bone surfaces in general, and because more radionuclide decays near growing bone surfaces—these seem to be most sensitive with respect to the production of osteosarcoma (Taylor *et al.*, 1983; Priest, 1987). Evidence of the latter is provided by the frequency of radiation-induced osteosarcomas at sites of high bone turnover (for example at the end of long bones).

Also, the distribution of the daughters of the parent radionuclides will influence the toxicity of the radionuclides. For example ^{90}Y produces a high-energy β-particle that can irradiate tissues much deeper into the bone marrow than the β-particle produced by the ^{90}Sr parent. Also, radium isotopes decay into a series of progeny all of which can potentially irradiate deep into the bone marrow due to the diffusion of radon gas away from the parent radionuclide. Finally, the incidence of bone sarcomas will be influenced by the deposition of layers of fibrous material on bone surfaces (Priest, 1990; Priest *et al.*, 1995). In theory, they should be protective because these layers contain no radiation-sensitive cells, but in practice the experience with the radium-dial painter populations suggests that the threshold dose for the production of these layers is similar to the lowest skeletal doses where osteosarcoma is seen (~10 Gy average skeletal dose). The lack of osteosarcoma at doses below this has given rise to the suggestion that there may be a threshold dose, below which osteosarcoma is unlikely (Lloyd *et al.*, 2000). The production of osteosarcoma may therefore be a result of misrepair to bone damaged by α-particles and not due to a lack of sensitivity to tumour induction of the target cells.

While classical radiodosimetry suggests that ^{226}Ra and other α-particle-emitting radionuclides on bone surfaces will result in the induction of leukaemia, there is little evidence for this in man. Evidence provided by studies of radium-dial painters that were exposed to ^{226}Ra and ^{228}Ra and large animal studies with radium suggest that leukaemia is a very unlikely consequence of the deposition of α-particle-emitting radionuclides on bone surfaces. The exception to this is the atypical aleukaemic leukaemia found in some radium chemists. This type of leukaemia is restricted to the bone marrow and may be associated with bone marrow stem cell failure at very high radiation doses. Together, the normal lack of leukaemia and the presence of leukaemia in patients that received Thorotrast (Becker *et al.*, 2008), which deposits throughout the bone marrow, suggests that the radiosensitive cells that give rise to leukaemia are not found close to bone surfaces. Clearly, radionuclides with high-energy β-particles and those that have decayed away from bone surfaces due to the diffusion of daughters do show leukaemia in human populations. In this way, both higher and lower doses of ^{224}Ra (daughter ^{220}Rn) injected into patients for the treatment of ankylosing spondylitis and tuberculosis do result in a small number of leukaemias (Wick *et al.*, 2008, 2009). The diffusion of radon (^{222}Rn) away from bone surfaces into the sinuses of the head is also considered to be the cause of head carcinomas seen in the radium-dial painters (Rowland *et al.*, 1978).

(b) Radionuclides that are chemically unrelated to normal bone components but bind to the matrix and/or mineral components of bone

This group of radionuclides includes many that are present in nuclear fuels and are potentially toxic to man. These include fuel components and activation products such as ^{239}Pu, ^{241}Am and ^{242}Cm (all actinons), and heavy-fraction fission products such as ^{144}Ce, ^{147}Pm and ^{152}Eu (all lanthanons). Human exposures are rare, and most of the toxicity data for these materials has been produced using laboratory animals. These show that these bone-surface-seeking radionuclides when present in the body produce a variety of tumour types—mostly skeletal tumours, leukaemia, and liver tumours (Humphreys *et al.*, 1985; Gillett *et al.*, 1987; Miller *et al.*, 2003). Human toxicological data exist only for plutonium within the population of former nuclear workers at Mayak within the former Soviet Union (Gilbert *et al.*, 2000; Koshurnikova *et al.*, 2000; Sokolnikov *et al.*, 2008). Experience with these suggests that exposures to plutonium isotopes (with ^{241}Am) result in a variety of tumour types, reflecting the distribution of these radionuclides in the liver and the skeleton. The ERR per unit dose of hepatic carcinoma and osteosarcoma in these workers is similar. Given the animal experimental data with a wide range of radionuclides and the human data with plutonium, any consideration of the toxicity of this group of bone seekers needs to consider both skeletal and extraskeletal deposits.

Lanthanons and actinons, like many other metal bone-seeking elements are multivalent and easily form complexes with organic molecules. It follows that radionuclides such as ^{144}Ce, a lanthanon, ^{239}Pu and ^{241}Am, both actinons, are present in the blood complexed to both large (transferrin and albumin) and small (citrate) molecules (Taylor *et al.*, 1987). These radionuclides are much less likely to be filtered by the kidney and excreted than those present as loosely bound ionic species in the blood (Talbot *et al.*, 1993). Plutonium in particular binds strongly to the iron-transport protein transferrin. In rats, 60% of uranium and 47% of radium are excreted in the first 24 hours after intake, but only 9% of americium and 6% of plutonium (Priest, 1990). Similar excretion patterns are seen in man. Because proteins tend to be retained within blood vessels, those radionuclides such as plutonium that are strongly bound to proteins tend to deposit most readily in those organs and tissues that have a sinusoidal blood supply. Sinusoids have a discontinuous endothelial lining, are irregular tubular spaces for the passage of blood, taking the place of capillaries and venules in the liver, spleen, and red bone marrow. The sinusoids form from branches of the portal vein in the liver and from arterioles in other organs including glands such as the adrenal glands and sex glands. The walls of the sinusoids are lined with phagocytic cells—macrophages that digest old erythrocytes and clear the bloodstream of toxins. Within the liver, both these cells and hepatocytes remove plutonium and other similar elements from the bloodstream (Priest, 1990).

In general, lanthanons and actinons deposit in either the liver or the skeleton on bone surfaces. No complete data set is available for man, but experiments with rodents suggest that bivalent metals (including the uranyl ion) do not deposit in the liver to any appreciable extent, that the trivalent metal ions (including the lanthanons, americium and curium) have a high fractional deposition in the liver, that the pentavalent ions, such as those of neptunium and protactinium, deposit to a higher extent in the skeleton than in the liver, but that tetravalent plutonium has a distribution that is intermediate between these extremes (Durbin, 1972). To a large extent, this deposition pattern is likely to result from differences in the charge density of the ion since research has shown that trivalent radionuclides deposit in rodents with a predictable pattern (Durbin, 1973). The research showed that there is a progressive shift towards

deposition in the skeleton with decreasing ionic size with large ions such as those of lanthanum and cerium depositing mostly in the liver, and small ions such as those of holmium and lutetium depositing mostly in the skeleton. In another experiment, Priest (2007) showed that the lanthanon ^{147}Pm and the actinon ^{242}Cm, which have the same valency (3^+) and the same ionic radius, behave identically in the body. Why this should be so is not clear. However, as binding to plasma proteins has been shown to be dependent on ion size and as the uptake of non-colloidal cations by the liver involves the active transport of metal ions across cell membranes, which is also likely to be an ion-size-dependent process, it has been speculated that these represent the distribution-determining processes (Durbin, 1973). In contrast, the uptake of metal ions by bone surfaces has been regarded as a less specific, passive process, independent of ionic size (Taylor *et al.*, 1971). Consequently, it is less likely to be important in determining the final distribution of the radionuclide (Priest, 1990). Another factor affecting the early distribution of bone-seeking radionuclides may be their rate of loss from the liver, as has been demonstrated in human volunteer studies using ^{237}Pu and ^{244}Pu (Etherington *et al.*, 2003). These indicate a high early uptake of plutonium by the liver (~90%) but a gradual loss thereafter to the skeleton. It would seem that plutonium cycles fast through the human liver, being alternatively released then recaptured, but that during each cycle a small amount of the radionuclide is captured by the skeleton producing the observed gradual transfer of radionuclide from liver to bone surfaces. A similar transfer is seen in animals (Priest, 1990).

The binding of radionuclides to plasma proteins also seems to affect the deposition pattern of these within the bone, at least in rodents. ^{239}Pu, which binds strongly to plasma proteins, seems unable to easily pass through the walls of blood vessels, and is preferentially deposited on internal endosteal bone surfaces adjacent to the blood sinusoids within the red bone marrow. In contrast, ^{241}Am (and other trivalent metal ions) – presumably because of the higher fraction bound to small plasma molecules such as citrate – diffuses more easily through the walls of blood vessels ,and deposits more evenly on all types of bone surface (Priest, 1990). The radionuclides also bind to surfaces at other sites of calcification including on dentinal surfaces adjacent to the pulp cavity in teeth and on mineralized cartilage surfaces. The mechanism of metal deposition on the bone surfaces is unclear but it is likely that a substantial fraction bind to phosphoproteins and other acidic proteins that are concentrated at the mineralized bone matrix front (Priest, 1990).

Subsequent to their deposition on bone surfaces, all long-lived lanthanons and actinons, as well as some other metals including iron and aluminium, will tend to remain on these surfaces unless removed by bone growth and remodelling processes. At lower levels of radionuclide accumulation, two outcomes are possible:

1) the contaminated bone surface can become buried by the apposition of new bone onto a growing bone surface;

2) bone surface deposits can be removed by osteoclasts during bone surface removal by these cells at sites of bone resorption.

Studies have shown that osteoclasts retain radionuclides such as ^{26}Al, ^{55}Fe, ^{239}Pu and ^{241}Am for a short time before they are passed to adjacent macrophages lying deeper within the bone marrow. The presence of macrophages containing ^{239}Pu and other similar radionuclides led to the speculation that the irradiation of surrounding bone-marrow cells could lead to the induction of leukaemia (Vaughan *et al.*, 1973), and myeloid leukaemia is seen in rodents treated with ^{239}Pu and ^{241}Am (Oghiso *et al.*, 1994; Ellender *et al.*, 2001). In contrast, it was not identified in the Mayak worker population exposed to plutonium (Sokolnikov *et al.*, 2008). Given that similar, albeit somewhat deeper buried, Thorotrast deposits in the red bone marrow do produce leukaemia, it is

not clear as to why this has not been observed for plutonium in humans.

Biokinetic studies suggest that plutonium remains in the bone marrow, associated with iron stores in ferretin, for approximately 80–100 days, and is then released in a soluble form into the surrounding tissue fluids. Much of this re-deposits on local bone surfaces maintaining the surface deposition pattern, but some returns to the bloodstream and most is either re-deposited in the liver, other organs, or is excreted. This small loss to excretion results in a slow loss of plutonium and similar metals from the skeleton giving half-times of retention that may exceed 50 years (ICRP, 1986).

Alternatively, if the radiation doses to bone surfaces are high following significant radionuclide intakes, such as seen in the radium-dial painters, the surfaces may become covered either with a layer of abnormal bone or by a layer of fibrous 'scar' tissue. Such pathologies have been seen in dogs following high actinon intakes, in baboons following intakes of plutonium, in humans following an accidental intake of ^{241}Am, and in the skeleton of a Mayak worker that had large occupational exposures to plutonium (Priest *et al.*, 1987, 1995; Suslova *et al.*, 2002).

While most ^{239}Pu and other bone-surface seekers are deposited in the liver and spleen, smaller amounts are deposited in a wide variety of tissues and these could potentially give rise to other tumour types. For example, a mice study using injected ^{242}Cm α-particles as a source of tissue irradiation produced a wide range of tumours that were in excess of those found in control animals–namely, mammary carcinoma, liver carcinoma, lung adenocarcinoma, uterine carcinoma, malignant lymphoma, liver histiocytic sarcoma, and lymph node histiocytic carcinoma (Priest *et al.*, 2010). All of these could be potentially caused by plutonium in humans but to date insufficient numbers of contaminated subjects are available to either confirm or reject this suggestion.

4.1.3 Non-bone-seeking radionuclides

This group includes important radiopharmaceutical/medical diagnostic agents (e.g. ^{11}C, ^{131}I, ^{18}F, ^{99m}Tc), other common commercially important radionuclides used by industry and for research (e.g. ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{210}Po), and radionuclides of inert gases that may become dissolved in tissue fluids (e.g. ^{85}Kr and ^{222}Rn). These are considered separately below.

4.1.4 Radiopharmaceutical/medical diagnostic agents

A wide range of radionuclides are used for either radiotherapy or for medical imaging (including for positron emission tomography (PET) and single photon emission computed tomography (SPECT)): ^{47}Ca; ^{11}C; ^{14}C; ^{51}Cr; ^{57}Co; ^{58}Co; ^{169}Er; ^{18}F; ^{67}Ga; ^{68}Ga; ^{3}H; ^{111}In; ^{123}I; ^{131}I; ^{59}Fe; ^{81m}Kr; ^{13}N; ^{15}O; ^{32}P; ^{153}Sm; ^{71}Se; ^{22}Na; ^{24}Na; ^{186}Re; ^{89}Sr; ^{99m}Tc; ^{201}Tl; ^{133}Xe; and ^{90}Y (NRPB, 1998). Some of these may be administered to patients as free ionic species: ^{18}F; ^{67}Ga; ^{123}I; ^{131}I; ^{59}Fe; ^{32}P; ^{22}Na; ^{89}Sr; ^{99m}Tc; ^{201}Tl; and ^{90}Y. The distribution of these within the body is a function of their affinity for different organs and tissues within the body, and many are bone-seekers (^{18}F, ^{67}Ga, ^{59}Fe, ^{32}P (as phosphate), ^{89}Sr, ^{99m}Tc (as pertechnetate)) with variable levels of uptake in other body tissues including the liver, spleen, and red bone marrow. Other radionuclides administered as ionic species either become more uniformly distributed among body tissues (e.g. ^{22}Na and ^{99m}Tc) or like ^{123}I deposit mostly within a single organ—in this case the thyroid gland. In addition, ^{3}H and ^{15}O may be administered in molecular form as water, and become uniformly distributed and irradiate all body tissues. Noble gas radionuclides ^{81m}Kr and ^{133}Xe are also administered as molecular species. These can be used either for lung perfusion studies following inhalation of the gases or following administration of the gases dissolved in water. Finally, ^{169}Er is administered

as a colloid and becomes distributed in the body with the same pattern as Thorotrast, with a high uptake by macrophages in the spleen, liver, lymph nodes, and red bone marrow. ^{99m}Tc can also be administered as a colloid and is deposited similarly. In contrast, ^{99m}Tc and ^{99}Tc as pertechnetate become more evenly distributed throughout the body with a higher uptake in the thyroid, salivary glands, stomach wall, colon wall, and liver (Beasley *et al.*, 1966).

In addition to the above, many radionuclides are used to tag (radiolabel) compounds that target specific cells, organs, and tissues within the body. In such cases, the distribution of the radionuclide within the body is not a function of the label employed, but of the moiety to which it is attached. Examples are many but some radiolabelled pharmaceuticals are currently used more than others – most today employ ^{99m}Tc as the radiolabel, because relative to other possible isotopes the radiation dose per investigation is lower. ^{99m}Tc-labelled exametazime crosses the blood/brain barrier, ^{99m}Tc-labelled sestamibi is used to study myocardial infarctions, ^{99m}Tc-labelled mercapto-acetyl-triglycine (MAG3) is retained within the bloodstream, and is used to assay renal function (Taylor *et al.*, 1988; Slosman *et al.*, 2001; Tanaka *et al.*, 2006). ^{99m}Tc-labelled bisphonates (methylene diphosphonate and dicarboxypropane diphosphonate) are deposited preferentially in the skeleton (Murphy *et al.*, 1997).

The recent explosion in the use of PET for diagnostic nuclear medicine has resulted in a range of new short-lived, cyclotron-produced, positron-emitting radionuclides being administered to patients at levels of administration of up to 400 MBq per investigation. These radionuclides include ^{11}C (half-life, 20 min), ^{13}N (half-life, 10 min) and ^{15}O (half-life, 2 min), but the most commonly used is ^{18}F (half-life, 110 min) (Shinotoh *et al.*, 1997; Young *et al.*, 1999). These radionuclides are sometimes used as labels for simple substances such as water, ammonia, and glucose. ^{18}F-labelled glucose and glucose derivatives (e.g. ^{18}F–fluorodeoxyglucose) are taken up, and in the case of ^{18}F–fluorodeoxyglucose retained, preferentially by metabolically active cells with a high requirement for glucose—including in the brain, liver, and most tumours (Young *et al.*, 1999). Other ^{18}F- (and ^{11}C-) labelled compounds, e.g. raclopride and 6-fluro-L-dopa, concentrate preferentially at dopamine receptors in the brain, and are used for PET brain scans (Shinotoh *et al.*, 1997).

Finally, some radionuclides have been used for radiotherapy (UNSCEAR, 2000). The efficient targeting of some tumour types with monoclonal antibodies labelled with radionuclides such as ^{211}At, which delivers a high α-particle dose to targeted cells, is sometimes possible (McDevitt *et al.*, 1998), but most radionuclides administered for radiotherapy use the ability of radionuclides to target cells by following metabolic pathways that exist for the transport of stable isotopes. In this way, ^{131}I is used to ablate the thyroid and treat thyroid cancer, ^{89}Sr and ^{186}Re-HEDP (-hydroxyethylidene diphosphonate) are used for the palliative treatment of skeletal metastases, and ^{32}P-orthophosphate to bind to bone surfaces and treat *polycythaemia vera*—a benign bone marrow disease (Harman & Ledlie, 1967; Spiers *et al.*, 1976; Tennvall *et al.*, 2000; Giammarile *et al.*, 2001; Orlandi *et al.*, 2001).

4.1.5 *Commercially important radionuclides used by industry and for research, and non-bone seeking fission products*

This group of radionuclides includes ^{3}H, ^{14}C, ^{32}P and ^{35}S, which are normal components of either all or a wide range of biomolecules. ^{3}H administered as the gas results in inconsequential doses to organs and tissues, and for this reason is widely used in industry to power emergency light sources. If it is administered as radiolabelled water, it mixes with cell and tissue fluids and delivers a much higher relatively uniform dose

to all body tissues until it is lost to excretion. In contrast, if ^{3}H-labelled compounds (including drugs administered to human subjects as part of the drug approval process) are administered then the distribution of dose within the body may well be highly heterogeneous with some target organs and tissues absorbing 90% or more of the total energy deposited in the body. Given the infinitely wide range of possible labelled biomolecules, it is not possible to specify any characteristic deposition pattern for ^{3}H-labelled compounds (reviewed by Hill & Johnson, 1993).

Similar considerations can be made for ^{14}C-labelled compounds that are also widely administered to human subjects within constraints recommended by the WHO for Category 1 human volunteer projects (maximum committed dose of 500 μSv per administration)—again it is not possible to specify any characteristic deposition pattern. Of more concern are intakes of ^{3}H and ^{14}C that are incorporated into food products following their release to the environment by nuclear industries and/or following the testing of thermonuclear devices. These will be digested in the gut, absorbed as labelled amino acids, fatty acids and carbohydrates, then metabolized within cells, and then either retained within the body as structural proteins, carbohydrates, etc. or excreted as carbon dioxide or water. Richardson (2009a) has developed a biokinetic model, the hydrogen, carbon, nitrogen and oxygen (HCNO) model that describes the distribution, retention and dosimetry of ^{3}H and ^{14}C intakes by the body. (NB: this model has been incorporated into the GenmodPC radionuclide dosimetry programme that is available from Atomic Energy of Canada Limited (AECL) for infants and children (Richardson & Dunford, 2001, 2003; Richardson, 2009b).

^{35}S, ^{32}P and P^{33} are used for research in laboratory studies to label specific biomolecules, but these are not normally administered to man. Again, it is not possible to specify any characteristic distribution pattern for these in the body. However, ^{32}P and ^{33}P administered as phosphate ions will be incorporated in hydroxyapatite (bone mineral) and other phosphated molecules including DNA, and ^{35}S administered as the sulfate ion will be incorporated widely into sulfated proteoglycans and glycoproteins that are present in bone, in cartilage, other connective tissues, and in mast cells (ICRP, 1979, 1993).

Other commercially important non-bone seeking radionuclides include ^{24}Na, ^{40}K, ^{137}Cs and ^{210}Po. ^{24}Na, ^{40}K and ^{137}Cs are all isotopes of alkali metals in Group 1 of the periodic table. ^{24}Na is produced from stable ^{23}Na by neutron capture, ^{40}K is a natural isotope and ^{137}Cs is mostly a long-lived decay product of the fission product ^{137}Xe. All of these isotopes have soluble ions that are, therefore, widely distributed within the body. In general, ^{24}Na will mix with stable sodium in the body and ^{137}Cs follows many of the metabolic pathways of potassium – including its natural radioactive isotope ^{40}K – and becomes relatively uniformly distributed until lost to excretion at a rate that is faster in women than in men (Melo *et al.*, 1997).

Finally, this group includes miscellaneous radionuclides: ^{60}Co, ^{106}Ru, ^{207}Bi, and ^{210}Po that are either used commercially or are important fission products. ^{60}Co is an important industrial radionuclide used in the manufacture of γ-beam sources for radiotherapy. The biokinetic properties of this essential element have been reviewed by Kim (2006) for the IPCS (WHO, 2006). Cobalt distribution and retention in man have been studied using ^{55}Co and ^{56}Co, and in rats using ^{57}Co and ^{60}Co. Following intravenous injection, the highest cobalt concentrations are found in the liver and kidney—with lower concentrations in other tissues including muscle, the brain, and testes. While much cobalt is rapidly cleared from the body some is retained, and is presumably incorporated within vitamin B12 (cobaltin), which is stored in the liver. In an interspecies comparison study using mice, rats, guinea-pigs, rabbits, dogs and baboons, large interspecies

differences in the lung clearance and retention of inhaled ionic cobalt were found (Patrick *et al.*, 1994). This study also identified the uptake of cobalt by cartilage structures. Relatively little is known about the biokinetics of ruthenium even though ^{106}Ru is an important, longer-lived fission product. The limited data available for rats (Dziura *et al.*, 1998) suggest that it is poorly absorbed from the gut, and is rapidly eliminated from the body. It has no specific affinity for any organ or tissue other than the kidney in which it accumulates to some extent. ^{106}Ru has a high-energy, β-emitting daughter ^{106}Rh, and has been used for the treatment of some eye conditions (Schueler *et al.*, 2006). The metabolism and retention of bismuth as ^{207}Bi in man has been studied (Newton *et al.*, 2001). A healthy male volunteer received an intravenous injection of ^{207}Bi as the citrate. After a rapid initial excretion, with 55% lost during the first 47 hours, principally in urine, longer-term losses were much slower, and 0.6% remained in the body at 924 days, when the contemporary rate of loss implied a half-life of 1.9 years. Integration of the retention pattern suggested that steady exposure to bismuth compounds could lead ultimately to a body content of 24 times the daily systemic uptake. The largest organ deposit was in the liver, which after 3 days contained approximately 60% of the contemporary whole-body content. This distribution is contrary to that previously described by the ICRP (1980), which envisages a terminal half-life in the body of only 5 days, and kidney as the site of the highest deposition. ^{210}Po is used in the manufacture of antistatic brushes as a relatively non-toxic α-particle source. However, when present in the body in ~GBq quantities, it has been shown to be toxic. The distribution and dosimetry of this isotope has been described by Harrison *et al.* (2007), and ^{210}Po is reported to be generally distributed throughout soft tissues in the body including in the liver, muscles and bone marrow, and is generally retained. No affinity of ^{210}Po for bone was identified.

4.1.6 Inert gases

Humans are potentially irradiated by both natural and anthropogenic radioisotopes of the noble gases. The most important are ^{85}Kr and ^{133}Xe released from nuclear reactors, and ^{220}Rn and ^{222}Rn, which are natural daughter products derived from uranium- and thorium-containing minerals. The latter are important because the inhalation of radon isotopes always contribute significantly to, and may dominate, the natural background dose to members of the public. Noble gases in Group 18 of the Periodic Table exist as diatomic molecules that are completely unreactive. It follows that the principle organ irradiated by exposure to noble gas radionuclides is to the lungs. However, krypton and radon are soluble in water so they will be absorbed by blood within the lungs, and circulated around the body where they may irradiate all tissues. Moreover, these gases are reported to be 16 times more soluble in lipids, and it is likely that adipose tissue and the bone marrow may be irradiated, particularly by ^{222}Rn, to a much greater extent than to other body tissues (Richardson & Henshaw, 1992). A similar distribution of dose may be expected following lung perfusion studies using other noble gas isotopes ^{81m}Kr and ^{133}Xe (Loken & Westgate, 1968; Yano *et al.*, 1970).

4.2 Mechanisms of carcinogenesis induced by all ionizing radiation

4.2.1 Introduction

The traditional approach to the mechanism of radiation-induced carcinogenesis is quite well explained in a recent review (Mullenders *et al.*, 2009), albeit in the context of low-dose radiation. Essentially, the radiation-induced damage to the genomic DNA, more or less regardless of the dose, stimulates a DNA-damage response, which attempts to affect repair of the damage before the cell goes into mitosis, whereupon residual damage

would be "fixed" and, if consistent with further cell division, replicated in all future generation of that cell. Cells with unrepaired or misrepaired damage are assumed to follow pathways through which they acquire the so-called "hallmarks of cancer" (Hanahan & Weinberg, 2000) or phenotypic features of malignancy, for example, loss of senescence and anchorage-free growth. In this approach, this process is assumed to be purely genetic, that is, these acquired features are attributable to mutations of a few specific genes, for example oncogenes or tumour-suppressor genes. This is the basis for the so-called "mutational theory of cancer"(Weinberg, 1998), and ionizing radiation, being a mutagenic agent, is considered a prime candidate for initiating such a process.

However, the mutational theory has been challenged (see for example, Soto & Sonnenschein, 2004; Bizzarri *et al.*, 2008). In addition, several recent developments in biology have placed a question mark over the validity and general applicability of the mutational theory.

First, genome-wide sequencing of several cancers of the same type have indicated that the carcinogenic process is not driven by a few mutated genes along a single pathway but by many genes along several pathways (Greenman *et al.*, 2007; Jones *et al.*, 2008; NCI, 2008). For example, in 24 pancreatic cancers, a total of 12 genetic pathways were identified (Jones *et al.*, 2008). The application of the newly developed high-throughput short-hairpin RNA (shRNA) screening is another powerful instrument that can reveal such multiple genetic changes and pathways in carcinogenesis (Bernards *et al.*, 2006).

Second, there is an emerging view that any cellular phenotype is more complex than assumed in the mutational theory, and is best represented by a pattern of active gene products (mainly proteins but also RNAs; Baverstock & Rönkkö, 2008; Huang, 2009). An essential prerequisite of this approach is to view the cell as a dynamic entity rather than as traditionally, a mechanistic entity. In the emerging view, phenotype is seen as an emergent property derived from the dynamic interaction of several (typically in the human cell, thousands) gene products, the profile of which can conveniently be described as a high dimensional dynamic attractor that endows phenotypic stability (attractors are a stable or stationary states of dynamical systems in which there is no continuum of stability, thus transitions between attractors are jumps). Two important features of this model are that transitions between phenotypes (attractor transitions) can take place without changes in gene sequence, i.e. can be purely epigenetic, and by several "pathways" as would be consistent with the evidence from genome-wide sequencing referenced above. The term "epigenetic," as used here, does not imply any specific mechanism such as chromatin marking but rather that the process is not related to specific changes to the DNA sequence.

On the basis of this concept of phenotype, both the initiation (Baverstock, 2000) and the progression (Brock *et al.*, 2009) of cancer can be seen as epigenetic and, in principle, reversible processes with the characteristic mutations accumulated as a consequence of the mutator phenotype typical for carcinogenesis (Bielas *et al.*, 2006). However, consequential mutations to specific genes could and most probably would serve to block the reversal of the carcinogenic process.

An important feature of this model, where initiation of cancer is concerned, is that it is not confined to radiation because the attractor transition is deemed to be a response to stress on the routine cellular processes, such as DNA-damage detection and repair (Baverstock & Rönkkö, 2008), and any agent capable of causing stress would be, in principle, able to cause cancer.

Third, the phenotypes of eukaryotes (including human cells) are mediated by the active protein products of the gene-coding sequences, and not the genes themselves. In most cases, the transcription of such a sequence produces an inactive

product that needs to be translated to a peptide, folded into a protein, which then often undergoes posttranslational modification and/or activation through, for example, phosphorylation (phosphoregulation). Thus, between the transcription of sequences and the presence in the cell of active proteins, there are many processes the control of which is far from clear. However, Beltrao *et al.* (2009) have shown in three strains of yeast that phosphoregulation provides a significant source of variation. Phosphoregulation derives from the binding of kinases at specific peptide sequences but there has to be present at least one other contributing controlling factor because cells exposed to ionizing radiation very rapidly (within a few minutes) show the presence of phosphorylated histone γ-H2AX sites (formed by such kinase activity) at strand breaks (Rogakou *et al.*, 1999). This is a clear example where purely epigenetic factors can intervene in influencing phenotype.

At the present state of knowledge, the carcinogenic process cannot be confidently attributed to either a purely genetic or purely epigenetic process and in all probability is a mixture of the two, the proportions differing from between cancer types and even case to case. This makes its perception as a mechanism, with the implication of determinism, problematic. However, the process is generally assumed to be a multistep process resulting from damage to a single cell with a normal phenotype, leading to an abnormal phenotype in which growth is not under normal control, and functionality is altered. Typically, tumour cells at the time of diagnosis carry large numbers of mutations but also may be heterogeneous in their gene-product profiles (Brock *et al.*, 2009). However, they have undergone many cell divisions and consequent processing of the molecular damage since their induction to the tumourogenic state, so the initial damage is likely to be obscured. Thus, the distinction between causal and consequential events in carcinogenesis can be difficult, if not impossible, to make.

Ionizing radiation, in addition to being capable of producing mutations– mainly by large-scale gene deletion – and gross chromosomal damage, can also induce epigenetic changes. For example, genomic instability as a late-occurring event appears several cell generations after irradiation, and results in a reduced ability to replicate the genotype faithfully (Kadhim *et al.*, 1992, 1994; Lorimore & Wright, 2003; Morgan, 2003a, b; Barcellos-Hoff, 2005). The events indicating instability include chromosomal aberrations, gene-sequence and mini-satellite mutations, and apoptosis. While many of these events can be seen as advancing cell transformation, an increase in apoptosis has been shown to have a protective effect against transformed cells *in vitro* (Portess *et al.*, 2007); these mechanisms could inhibit the neoplastic process. Molecular and cellular data indicate that the frequency of occurrence of genomic instability in relation to dose is such that it will not be due to specific genes affected by the initial ionizing event (Baverstock, 2000). It has also been proposed, given the similarity of processes leading to tumour formation and that of genomic instability, that genomic instability may be a potential candidate for the initial event of tumourigenesis (Baverstock, 2000; Little, 2000).

The bystander effect (Nagasawa & Little, 1992) is another feature of the influence of ionizing radiation on cells that might influence tumour formation through epigenetic processes. Cells that have not been subject to direct irradiation can exhibit the phenotypic features of genomic instability if they are in the neighbourhood of cells that have been subject to ionizing events (Lorimore *et al.*, 1998). This effect can be mediated through various mechanisms including cell-to-cell communication or signalling by way of gap junctions (Azzam *et al.*, 1998, 2001; Bishayee *et al.*, 2001), and secretion of chemicals into the intracellular matrix (Mothersill & Seymour, 1997a, b; Barcellos-Hoff *et al.*, 2005;

see Section 4.2.6). Bystander effects and genetic instability have also been observed after exposure to other carcinogenic agents, e.g. UV (Dahle & Kvam, 2003) and some chemicals (Asur *et al.*, 2009). In addition, there may be abscopal effects, where irradiation of an organism at a specific site remotely mediates cellular or phenotypic responses (Mancuso *et al.*, 2008). Some of these abscopal effects may be due to clastogenic factors generated by radiation in blood plasma (Emerit, 1990), and result in damage that is similar to that caused directly by radiation in tissues through which the plasma passes.

The bystander effect implies that the specific environment, e.g. the niche, in which a stem cell grows, has an important influence on its regulation (Scadden, 2006). This implies also the opposite process when a phenotypically abnormal cell may disrupt cells in its environment. In addition, other host factors – some of which are influenced by aging – will have an impact on the phenotypic state of an irradiated cell, usually to facilitate the return to the initial phenotypic state. Thus, there is a dynamic interplay between individual cells and their tissue and host environments, which is necessary for sustaining tissue integrity, but which – if disrupted – can lead to disease, including tumour formation (Li & Neaves, 2006).

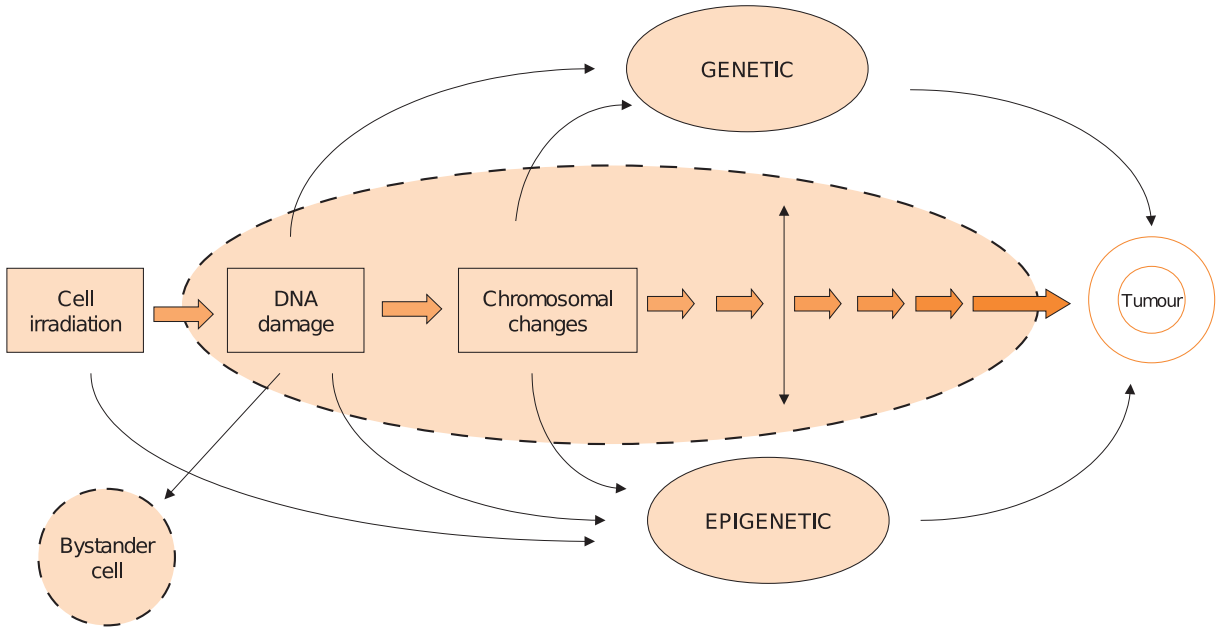
Therefore, it would appear that there are several mechanisms for cancer development, and that radiation effects may play a role in many aspects of carcinogenesis, that is in the acquisition of genetic mutations and epigenetic changes, and in the interactions between nearby and distant cells in an organism. This is likely to proscribe a detailed description at the molecular level of the events that intervene between the normal and malignant phenotype. Fig. 4.1 gives a schematic representation of this emerging concept for carcinogenesis.

4.2.2 The deposition of ionizing energy

Interactions of ionizing radiations with molecular structures in mammalian cells induce many different types of molecular damage, which subsequently lead to a diversity of cellular responses, including cell killing, chromosomal aberrations, mutations, and cell transformation (BEIR VI, 1999; UNSCEAR, 2000; ICRP, 2002, 2005, 2007; BEIR VII, 2006). Their efficiency in causing damage and subsequent biological effects is related not only to the amount of energy transferred per unit mass and rate of transfer, i.e. the absorbed dose and dose rate, but also to the micro-distribution of energy, which is determined by the type of radiation. Typically, the effectiveness per unit of absorbed dose for different biological end-points increases with the linear energy transfer (LET) up to a maximum at approximately 100 keV/μm. For different types of ionizing radiation, the numbers of charged particles per unit dose and the structures of their radiation tracks are different at the tissue, cellular, and subcellular levels. Ionizing radiation deposits energy in the form of atomic and molecular ionizations and excitations from the interaction of the individual moving particles with the medium. The highly structured spatial pattern of interactions from a particle and its secondary particles is termed the *radiation track* of the particle.

Generally speaking, most of the energy deposition is produced by secondary or higher-order electrons set in motion following interactions of the primary radiation, be it a photon (X-ray or γ-ray), a neutron, or a charged particle. The energy depositions occur in clusters along the trajectories of electrons and charged particles, and the resulting non-homogeneity of the microdistribution can be substantial. The microscopic energy depositions and the track structure vary greatly with the stochastic nature of each atomic interaction (ICRU, 1983; Kellerer, 1985; Goodhead, 1987, 1992). A diagrammatic representation

Fig. 4.1 Schematic representation of many aspects of carcinogenesis induced by ionizing radiation

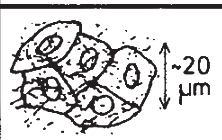
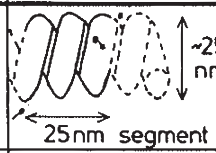
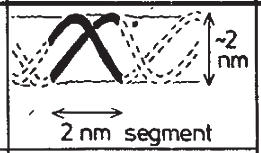
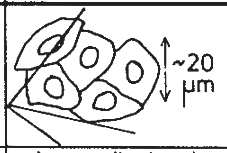
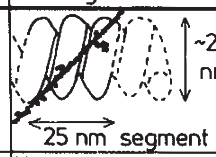
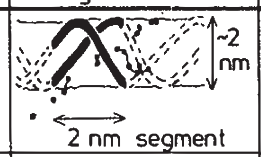
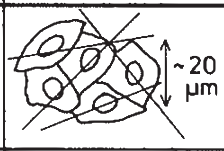
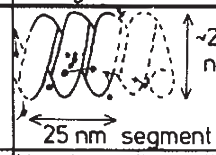
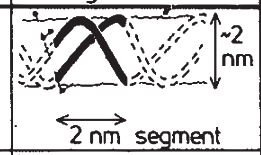


of the microscopic patterns of radiation tracks associated with external γ-rays, α-particles from internal ^{220}Rn decays, and external 10-MeV neutrons is given in Fig. 4.2.

All ionizing radiation ultimately leads to the production of electrons, through which energy will be deposited. X-rays and γ-rays interact within tissues producing fast electrons that interact with atoms or nuclei, producing additional electrons as they slow and deposit energy. Charged particles such as α-particles and protons also interact to produce a trail of secondary electrons along the path of the primary particles. Uncharged neutrons also interact within tissue and deposit their energy via lower-energy charged particles such as protons, deuterons, α-particles and heavy-ion recoils, in addition to interactions leading to the production of γ-rays. These charged particles ultimately lead to energy deposition via secondary electrons. Therefore, energy deposition by way of electrons is common to all ionizing radiations, including neutrons.

The effects of low-energy electrons (0.1–5 keV) can be studied using ultra-soft X-rays. Data from several laboratories show that low-energy electrons from ultrasoft X-rays are more effective in producing a wide range of biological end-points than equal doses of conventional X-rays or γ-rays (reviewed by Goodhead & Nikjoo, 1990; Goodhead, 1994; Hill *et al.*, 2001; Hill, 2004). The end-points include DNA double-strand breaks, cellular inactivation, chromosomal aberrations, mutations, and cell transformation. This greater effectiveness is due to the increased local ionization density produced by low-energy electrons, which results in greater clustering of events on and around the DNA. Low-energy electrons are not unique to ultra-soft X-rays, but are produced by all ionizing radiations (Goodhead, 1991; Chetioui *et al.*, 1994; see also Section 1). The percentage of the absorbed dose deposited by low-energy electrons (0.1–5.0 keV) increases from ~33% for ^{60}Co γ-rays to 78% for β-particles emitted by ^{3}H (Nikjoo & Goodhead, 1991). Low-energy electron track-ends have been proposed as the biologically critical component of low-LET radiation rather than the isolated ionization and excitation events along the path

Fig. 4.2 Microscopic consequences of 1 cGy absorbed dose

	Whole tissue	Individual cells	Chromatin fibre (total ~5 cm per cell)	DNA (total ~2 m per cell)	Mean number lethal lesions per cell
External γ rays					~0·001
Dose uniformity	Uniform Dose = 1 cGy	~ Uniform Dose ≈ 1 cGy	Very large fluctuations Doses = 0 to ~10^3 Gy	Very large fluctuations Doses = 0 to ~10^6 Gy	
Mean number of tracks	10^9 gram^{-1}	~ 50 cell^{-1} No cells unirradiated	~10^{-6} segment^{-1} ~20 segments hit cell^{-1}	~10^{-8} segment^{-1} ~10 segments hit cell^{-1}	
Internal ^{220}Rn (3 α's)					~0·01
Dose uniformity	Variable Doses = 0 to ~2 cGy	Large fluctuations Doses = 0 to ~30 cGy	Very large fluctuations Doses = 0 to ~10^4 Gy	Very large fluctuations Doses = 0 to ~2 x 10^6 Gy	
Mean number of tracks	~10^7 gram^{-1}	~ 0·1 cell^{-1} ~90% of cells unirrad.	~6 x 10^{-7} segment^{-1} ~1 segment hit cell^{-1}	~10^{-8} segment^{-1} ~10 segments hit cell^{-1}	
External 10 MeV neutrons					~0·005
Dose uniformity	Uniform Dose = 1 cGy	Large fluctuations Doses = 0 to ~5 cGy	Very large fluctuations Doses = 0 to ~5 x 10^3 Gy	Very large fluctuations Doses = 0 to ~10^6 Gy	
Mean number of tracks	~10^7 gram^{-1}	~ 1 cell^{-1} ~37% of cells unirrad.	~4 x 10^{-6} segment^{-1} ~8 segments hit cell^{-1}	~10^{-8} segment^{-1} ~10 segments hit cell^{-1}	

Adapted from Goodhead (1987). Copyright Elsevier.

of fast electrons (Goodhead & Nikjoo, 1990; Botchway *et al.*, 1997).

Recent studies have also proposed that inner-shell ionization events in DNA that lead to the production of low-energy Auger electrons may be a major factor in DNA damage and cell death. (Fayard *et al.*, 2002, Boissière *et al.* 2007; NB: following the removal of an inner-shell electron, an electron from a higher energy level may fall into the vacancy, resulting in a release of energy. This is either released in the form of a characteristic X-ray or the energy can also be transferred to another electron, which is ejected from the atom, called an Auger electron.)

^{3}H also leads to the production of low-energy electrons. It decays solely by β decay, emitting an electron with a range of energies of up to a maximum of 18.6 keV (mean energy of 5.7 keV) with an average track length of 0.56 μm and a maximum track length of 6 μm (Carsten, 1979). A subgroup of the Advisory Group on Ionizing Radiation has recently reviewed the risks associated with ^{3}H (HPA, 2007); it noted that tritiated water has generally been observed to be between 1–2 times more effective than a similar dose of orthovoltage X-rays, and 2–3 times more effective than γ-rays, in producing a range of cellular and genetic end-points (including cellular inactivation and induction of DNA strand breaks,

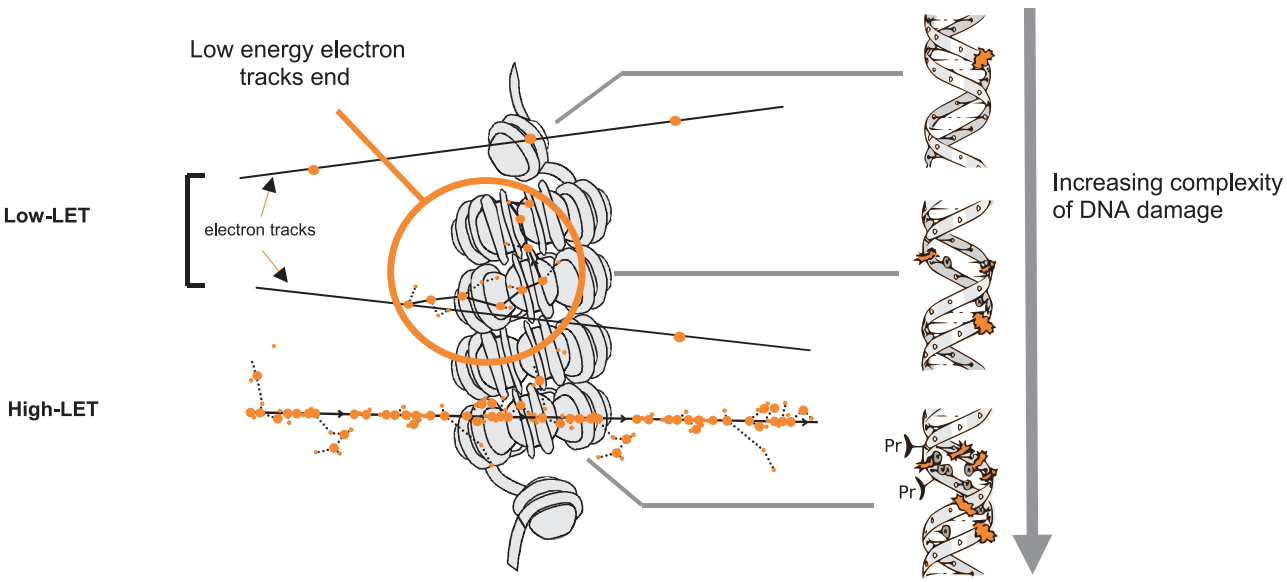
chromosomal aberration formation and mutation). The potential for tritiated DNA precursors to result in substantially higher doses and effects than other forms of tritium has long been recognized, and has received considerable attention in terms of experimental studies and theoretical considerations (e.g. ICRP, 1979; NCRP, 1979). Exposure to ^{3}H has also been observed to produce chromosomal aberrations in the lymphocytes of the exposed person (Lloyd *et al.*, 1986, 1998).

For many biological end-points, nuclear DNA is believed to be the critical target of ionizing radiation (UNSCEAR, 1993). Evidence for this comes from the greater biological effectiveness of radionuclides incorporated into nuclear DNA, rather than more generally distributed (Hofer *et al.* 1975, Hofer & Warters, 1985) in the cell, along with cell irradiation that included, rather than excluded, the nucleus (e.g. Munro, 1970). In addition, many studies in cells and animals deficient in DNA-damage response (processing/repair) have shown an increase in the frequency of radiobiological effects, including cancer induction (UNSCEAR, 1993, 2000; ICRP, 1998; BEIR VII, 2006). Ionizing radiation can result in DNA damage, either directly by ionization of its constituent atoms, indirectly by reactions with free radicals produced by interactions with water molecules – most notably the hydroxyl radical, which can result in a DNA strand break – or combinations of these two. Hydroxyl radicals will typically only diffuse a few nanometres, thus preserving the spatial structure of the radiation tracks. Subsequent reactions may lead to the production of longer-lived radicals, which may diffuse over longer distances, and are unlikely to contribute to the production of clustered DNA damage. Ionizing radiation can induce a range of different types of molecular damage in DNA, such as base damage, single-strand breaks, double-strand breaks, DNA–protein cross-links, and combinations of these. The pattern and frequency of these lesions is determined by the clustering of ionization events, which ultimately produces clustering of damage over the dimensions of the DNA helix and larger. The more complex forms of damage are unique to ionizing radiation, and are not seen spontaneously or with other DNA-damaging agents. Analyses of track structures caused by different types of radiation show that clustered DNA damage more complex than a simple double-strand break can occur at biologically relevant frequencies with all types of ionizing radiation (Goodhead, 1987; Brenner & Ward, 1992; Goodhead, 1994). Such clustered damage in DNA is produced mainly within a single track, with a probability that increases with increasing ionization density (see Fig. 4.3).

The correlation of damage with a single track can also occur over larger dimensions in a cell, including within the chromatin structure, among chromosomes and among adjacent cells, if the particle range is sufficient.

At the level of the DNA and its structure, most of the information comes from theoretical simulations (Pomplun *et al.*, 1996; Nikjoo *et al.*, 1997). These led to quantitative estimates of the DNA-damage spectrum, which includes base damage, single-strand breaks, simple double-strand breaks, and complex double-strand breaks (double-strand breaks with additional damage within a few base pairs). Calculations and experimental measurements showed that the total yield of double-strand breaks per unit of absorbed dose is fairly independent of LET for a variety of common radiations. However, theoretical simulations have predicted that the percentage of complex double-strand breaks (defined as having additional strand breaks within 10 base pairs), which is 20–30% from low- to medium-energy electrons (similar to those produced by X-rays and γ-rays), will increase with increasing ionization density (LET) of the radiation to approximately 50% for 0.3-MeV protons, and to more than 70% for high-LET 2-MeV α-particles (Nikjoo *et al.* 2001, 2002). The number of double-strand breaks classified as complex increases to approximately 96% for 2-MeV α-particles if double-strand

Fig. 4.3 Schematic illustration of the clustering of ionization events and the ensuing DNA damage by high-LET and low-LET radiation tracks



Adapted from Goodhead (1988, 1994). Reproduced by kind permission of Mark Hill, University of Oxford, United Kingdom

breaks with additional base damage are also classified as complex. Not only is there an increase in the frequency of complex double-strand breaks with increasing LET, but also an increase in the overall complexity of the spectrum of damage produced. The ultimate biological consequence is dependent on how this damage is processed by the cell, whether it is repaired and with what fidelity. It has been plausibly hypothesized that the more complex components of the damage spectrum are less repairable, and therefore dominate the biological response (Goodhead, 1994). Under this hypothesis, the differences in biological effectiveness between radiations of different quality, such as α-particles, protons and X-rays, for a given absorbed dose and a range of biological end-points (including cell survival, gene mutation, chromosomal aberration induction and transformation) are due predominantly to the greater yield of complex damage, and its greater degree of complexity from high-LET radiations (Goodhead, 1994; Ward, 1994). Model systems have shown that clustered DNA damage also compromises the effectiveness of DNA repair and can lead to an increase in mutation frequency (Gulston *et al.*, 2004; Pearson *et al.*, 2004). Clustering of damage is not just confined to DNA but can occur in all biomolecules within the cell.

There are also significant differences in track structure on the cellular/nuclear scale. When a cell is traversed by an α-particle, the energy deposition is highly heterogeneous across the cell with a greater probability of correlated damage and double-strand breaks within a single chromosome or adjacent chromosomes along the path of the particle. By use of R-banding and fluorescence in-situ hybridization (FISH) it was demonstrated that the traversal of the cell nucleus by a single particle with LET above 50 keV/μm efficiently induced complex chromosomal rearrangements (Sabatier *et al.*, 1987; Testard *et al.*, 1997; Cornforth, 2006; see Fig. 4.4 and 4.5). Studies with Multiplex fluorescence in-situ hybridization (mFISH) show that commonly four and up to a maximum of eight different chromosomes were observed to be involved in rearrangements following a nuclear traversal

Fig. 4.4 mFISH "painted" human metaphase (A) and karyotype (B) chromosomes showing the characteristic and extensive chromosomal damage induced after α-particle irradiation. The chromosome exchange is very complex, involving six chromosomes (4, 8, 13, 18, 18, and 21) with a minimum of seven breaks (white arrows). Lymphocytes in G_0 of the cell cycle were exposed to 0.5 Gy of α-particles from α ^{238}plutonium source (mean tracks per cell = 1).

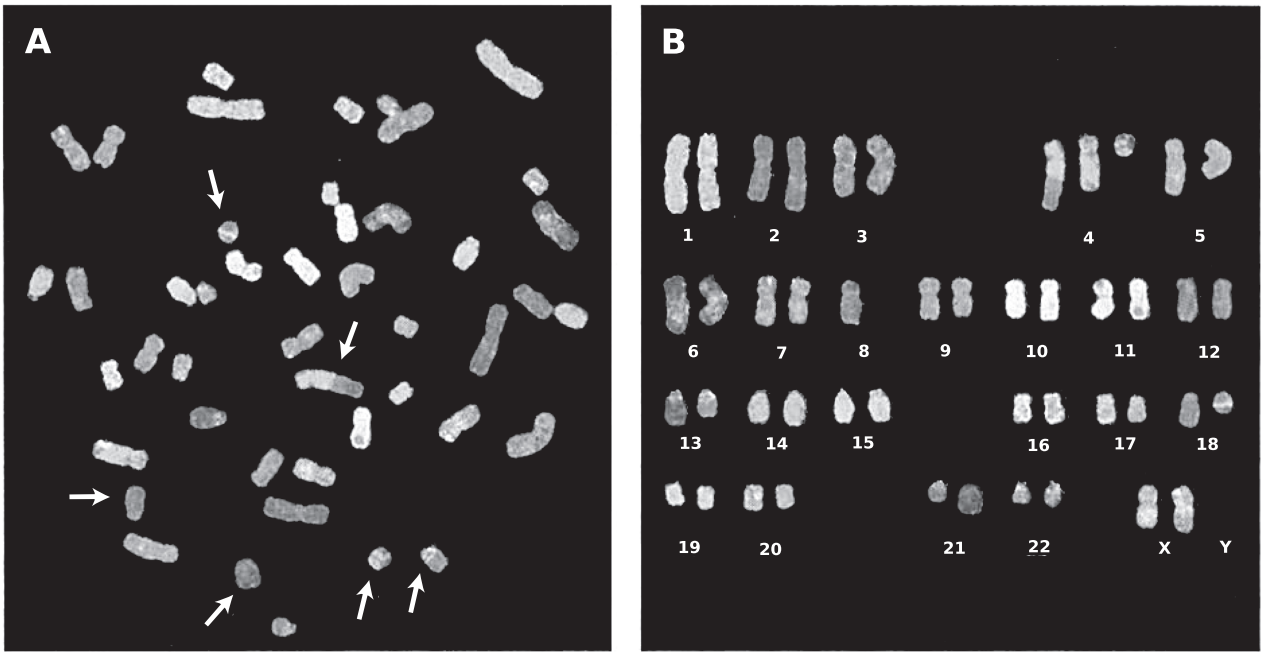


Image courtesy of Rhone Anderson, Brunel University, West London, UK
Image adapted from Savage (2000). Cancer: Proximity matters. *Science,* 290:62–63

of a human peripheral blood lymphocyte by an α-particle (Anderson *et al.*, 2002, 2006), with a similar response seen in human CD34$^+$ haematopoietic stem cells (Anderson *et al.*, 2007). This is in contrast to the production of mainly simple rearrangements between two chromosomes observed for low doses of low-LET X-rays.

In a study of a small group of workers with a large body burden of α-particle-emitting plutonium, unstable cells containing non-transmissible complex aberrations (exchanges involving three or more breaks in two or more chromosomes) were found in all the plutonium-exposed subjects when their lymphocytes were analysed by use of mFISH (Anderson *et al.* 2005). In a separate study, stable intrachromosomal rearrangements in lymphocytes of former nuclear-weapon workers exposed to plutonium were seen. Many years after exposure, more than half of the blood cells of healthy plutonium workers contained large (> 6 Mb (mega base pairs)) intrachromosomal rearrangements in amounts that correlated with the plutonium dose to the bone marrow, while very few intrachromosomal aberrations were observed in control groups (Hande *et al.*, 2003).

The consequence for background radiation is that individual cells may receive no track at all or only single tracks, well isolated in time (approximately 1 mGy/year for low-LET radiation). Each cell nucleus in a tissue will experience on average approximately one electron track per year (assuming a spherical nucleus of 8 μm diameter). Increasing the tissue dose above 1 mGy will essentially increase the nuclear dose to all cells. In comparison, with 1 mGy of α radiation (such as

Fig. 4.5 mFISH karyotype showing an α-particle-induced complex involving chromosomes 3, 7, 8, 11, 12, and 18 (arrows).

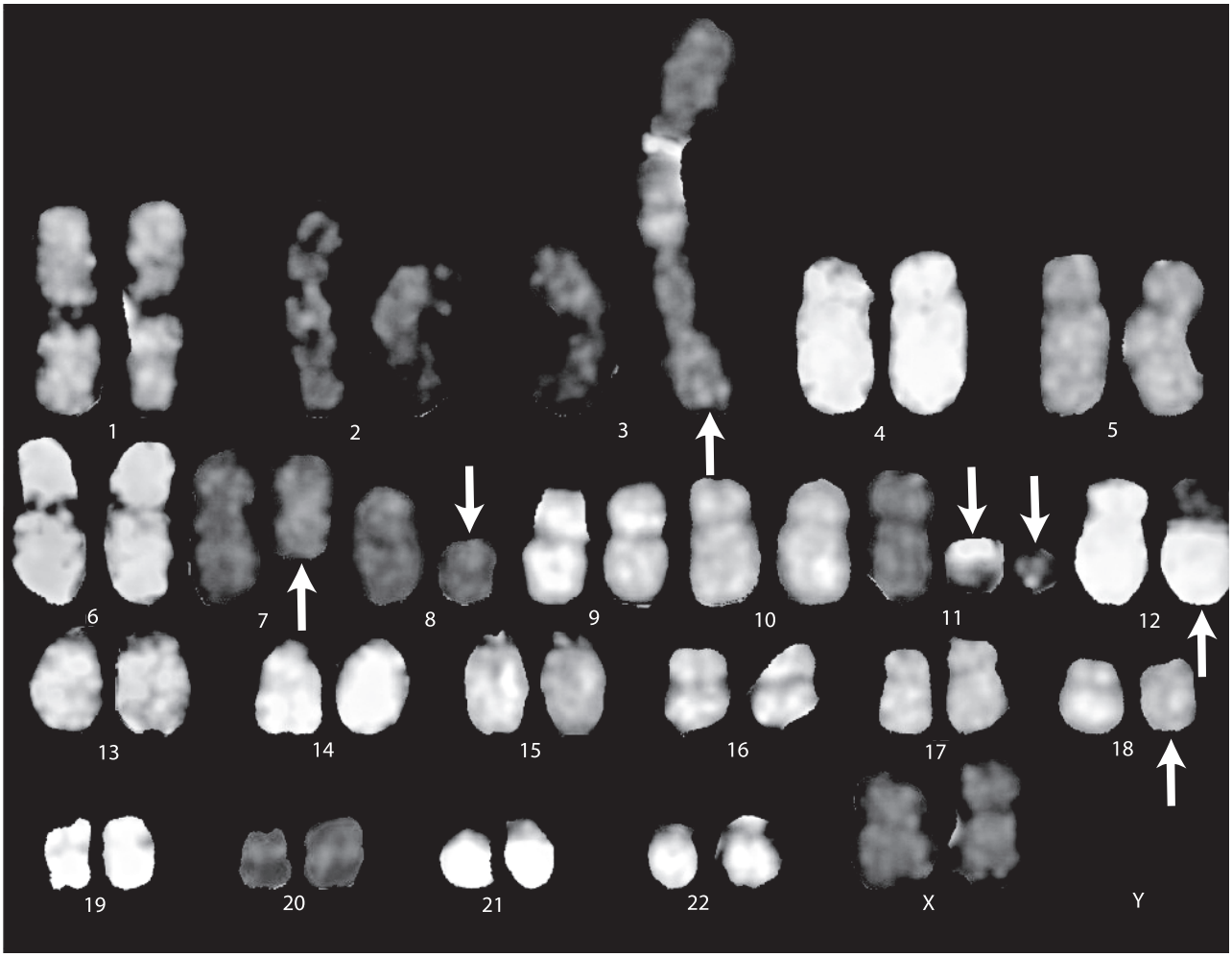


Image adapted from Anderson *et al.* (2002). Copyright 2002 National Academy of Sciences, USA

from radon) only about 0.3% of the nuclei in the irradiated tissue is hit by a track, the remaining 99.7% are totally un-irradiated. However, the cells that are traversed will receive a substantial amount of energy deposition, with an average nuclear dose of approximately 370 mGy for the traversed cell, with individual nuclei potentially receiving up to 1 Gy. Therefore, for high LET tracks, it is the fraction of cells traversed that varies with tissue dose, rather than the energy deposited in the nucleus from single-track events (Goodhead, 1992).

While external irradiation with photons is highly penetrating and will often result in a relatively uniform dose-distribution across the absorbing tissue, emission from internal radioisotopes typically occurs from specific locations occupied by the emitting nuclide. This will often lead to a non-uniform dose to the body, especially if the emitted radiation has only a short range (for β-particles, from centimetres down to microns; for α-particles, typically less than 80 μm). The overall exposure is dependent on several factors. Biokinetic models (ICRP, 1989, 1993, 1994, 1995, 1996, 2001) are used to model

the spatial and temporal uptake of radionuclides, their subsequent distribution, and their ultimate excretion, to calculate the total number of radioactive decays within specified tissues. Dosimetry models (Eckerman, 1994) are subsequently used to calculate the deposition of energy in organ or tissue, taking account of the physical characteristics of the isotope (type and emission energy, and any radioactive progeny).

In the case of Auger decay, most Auger electrons are confined to single cells or subcellular compartments. The biological effects vary greatly depending on whether the Auger emitter is attached to DNA, free in the nucleus or in the cytoplasm. Large differences in energy deposition, even at the organ and tissue levels, can occur with different radionuclides or radiolabelled compounds, because of the heterogeneous distribution of radionuclides, the stochastic nature of the radionuclide-decay processes, and the emission of short-range radiation (i.e. α-particles, low-energy β-particles, Auger electrons, and low-energy X-rays). Detailed knowledge of the cellular and subcellular localization in the relevant tissue of the particular radionuclide and any associated molecule may be relevant before a full assessment can be made of the implications of the internal emitter. Additional mechanisms of DNA-damage induction may result from the presence of the nuclide within the cell. These include molecular effects after transmutation of a radionuclide to a different progeny, recoil of the progeny nucleus, and charge accumulation on the progeny atom after an Auger cascade. If the decaying atom is appropriately positioned, the recoil nucleus may have considerable energy and can cause substantial cellular damage. The effects of the recoil nucleus are not considered in this *Monograph*. The induced damage can be misrepaired and have cellular consequences (IARC, 2001).

4.2.3 Processing of radiation-induced genetic damage at the cellular level

As discussed above, ionizing radiation is able to produce DNA double-strand breaks, DNA single-strand breaks, and a variety of base damages, and combinations of these to form a unique type of damage in which multiple lesions are encountered within close spatial proximity. Even a single track of ionizing radiation through a cell is likely to induce these unique, clustered damages. This type of damage is unlikely to be frequently generated endogenously or by other exogenous agents (ICRP, 2006).

Cells have a vast array of damage-response mechanisms, including pathways of DNA repair, the operation of cell-cycle checkpoints, and the onset of apoptosis. These processes facilitate the repair of DNA damage and the removal of damaged cells; however, these mechanisms are not error-free. It is generally accepted that unrepaired or misrepaired double-strand breaks are the principal lesions of importance in the induction of chromosomal abnormalities and gene mutations (Goodhead, 1994; Ward, 1994). Two mechanistically distinct pathways for double-strand-break repair have been described: non-homologous end-joining, which requires little or no homology at the junctions and is generally considered to be error-prone, and homologous repair that uses extensive homology and is considered error-free. A third process is single-strand annealing, which uses short direct-repeat sequences (see ICRP, 2006). Base damage is repaired via the base-excision-repair pathway, the latter stages of which repair single-strand breaks. Clustered radiation-induced lesions pose a particular problem; and currently, emerging evidence suggests that closely spaced lesions can compromise the repair machinery. For instance, the ability of glycosylase to recognize and remove a damaged base is impeded by the presence of a nearby single-strand break in the opposite strand (David-Cordonnier *et al.*, 2000, 2001). On this

basis, there is no strong evidence for a radiation dose below which all radiation-induced damage can be repaired with fidelity. While many of the cells containing such radiation-induced damage may be eliminated by damage-response processes, it is clear from the analysis of cytogenetics and mutagenesis that damaged or altered cells are capable of escaping these pathways and propagating (ICRP, 2006).

The idea that molecular damage directly caused by ionizing radiation might be a detectable marker of radiation exposure in tumour cells at diagnosis has been extensively investigated, particularly in relation to the radiation-induced childhood thyroid cancers following the Chernobyl accident. However, such a marker has not been conclusively observed. Likewise, in a recent study looking at the expression of cell cycle regulatory proteins, no such biomarkers were found to differentiate between radiation-induced and sporadic papillary thyroid carcinoma (Achille *et al.*, 2009).

However, specific mutations of the *TP53* gene in human radiation-induced sarcomas have been found. About half of the radiation-induced sarcomas contained a somatic inactivating mutation for one allele of *TP53*, systematically associated with a loss of the other allele, and some other features may be related to exposure to ionizing radiation. (Gonin-Laurent *et al.*, 2006).

A study of eight radiation-induced solid tumours has described a common cytogenetic profile after irradiation: the occurrence of chromosome imbalances, creating large loss of hereozygosity. Such a profile is also observed in radiation-induced tumours whereas spontaneous cases of the same tumour type are characterized by a specific balanced translocation. These results support a proposed mechanism for cancer induction where accumulated recessive damage in the genome is unmasked (for example after telomere loss), allowing transcription of the mutated allele, which could provide a cellular proliferation advantage (Chauveinc *et al.*, 1999; Ayouaz *et al.*, 2008).

In a mouse model for radiation-induced acute myeloid leukaemia, the loss of specific genetic material (*Sfpi1*/PU.1) on chromosome 2 was observed to be correlated with strong growth advantage (Bouffler *et al.*, 1997; Peng *et al.*, 2009). This is however a feature of the model, missense mutation at codon 235 in the DNA-binding transcription factors Ets domain of the PU.1, which was not observed in human therapy-related acute myeloid leukaemia (Suraweera *et al.*, 2005).

4.2.4 Genomic instability

Situations in which the cellular capacity to repair damage caused by irradiation is saturated have the potential of stressing the cell, which leads to the modification of the genome-wide gene-product profile, thus precipitating a phenotypic transition without specific, or indeed any, genotypic damage. This is postulated to be a possible origin of genomic instability (Baverstock & Rönkkö, 2008).

Genomic instability has also been attributed to an anti-inflammatory-type response that is both persistent and causes a predisposition towards malignancy (Lorimore *et al.*, 2003; Barcellos-Hoff *et al.* 2005).

Genomic instability could be linked to the loss of telomere maintenance. Many studies have described the presence of dysfunctional (too short) telomeres as a universal mechanism in the early phase of cancer development (Rudolph *et al.*, 1999; Meeker *et al.*, 2004, Raynaud *et al.*, 2008; Batista & Artandi, 2009). It has been proposed that short telomeres will contribute to genomic instability in the aged progeny of irradiated cells (Sabatier *et al.*, 1992, 1995; Martins *et al.*, 1993, Ayouaz *et al.*, 2008). Moreover, dysfunctional telomeres are associated with radiation-induced genomic instability and radiosensitivity (Goytisolo *et al.*, 2000; McIlrath *et al.*, 2001; Williams *et al.*, 2009). Even

after telomerase activation, the loss of telomeres can generate most of the types of chromosomal rearrangements detected in cancer cells such as gene amplification and chromosome imbalances (Murnane & Sabatier, 2004; Sabatier *et al.*, 2005).

4.2.5 Adaptive response

Low-LET radiation has been shown to modulate gene expression in a dose-dependent manner (reviewed by Brooks, 2005), and to induce an adaptive response to a test dose given after an adaptive dose in the mGy range (Coleman *et al.*, 2005). An adaptive response has also been seen in a pKZ1 mouse-prostate model when the test dose of 1 Gy was given before the adaptive dose of 0.01–1 mGy (Day *et al.*, 2007). An adaptive response had been shown in certain model systems *in vitro* to increase the repair of chromosomal breaks (Broome *et al.*, 1999), and to modulate the cellular level of certain redox pathways (Spitz *et al.*, 2004). The adaptive response after an adaptive dose given alone (i.e. in the absence of a challenge dose) reduces the frequency of radiation-induced neoplastic transformation in human and rodent cells *in vitro* (Azzam *et al.*, 1996; Redpath & Antoniono, 1998; Mitchel, 2006). In C57BL6 and CBA mice, such an adaptive response results in an increased latency of spontaneous and radiation-induced tumours (Mitchel *et al.*, 1999, 2003, 2004). This is proposed to be part of a general cellular stress response, such as that against heat stress, that appeared very early in evolution (Mitchel, 2006). In mammalian cells, including human cells *in vitro*, and in mice *in vivo*, the adaptive response is induced within a dose range from about 1–100 mGy, although this can vary with tissue type (Azzam *et al.*, 1996; Redpath & Antoniono, 1998; Mitchel *et al.*, 2003, 2004). Above or below these doses, increased cancer rates have been seen in C57BL6 mice *in vivo* (Mitchel *et al.*, 2004, 2008). Protective adaptive responses to radiation in mammals are dependent on a fully or partially functional *Tp53* gene, and do not occur in *Tp53*-null cells (Sasaki *et al.*, 2002) or animals (Mitchel, 2005). [The Working Group noted that protective effects as described here were discussed but not endorsed by BEIR VII (2006) and ICRP (2007), but supported by the French Academy of Sciences (2005). The Working Group concluded also that although an adaptive response has been shown, the final impact on cancer risk cannot be clearly determined because it depends on many factors including dose, time and the genetic make-up of the irradiated organism.]

4.2.6 Intercellular communication and the bystander effect

Tissues in multicellular organisms are self-organized "colonies" of communicating cells that mutually reinforce each other's phenotypic state (Park *et al.*, 2003). Radiation-induced transitions of individual cells to abnormal phenotypic states has been shown to disrupt these essential communications through the bystander effect, which may lead to loss or gain of function, and thus modify behaviour at the tissue level (Barcellos-Hoff, 2001). Thus, although tumour formation is recognized to have been initiated in a single cell, it is influenced by neighbouring cells for its full development. One consequence of this inter-cellular communication is the bystander effect in cells subject to ionizing radiation (Nagasawa & Little, 1992) where chemical signalling from an irradiated cell influences the phenotype of un-irradiated neighbouring cells, presumably through modification of the genome-wide protein profile or through modification of the genotype by some indirect means. Bystander cells thus exhibit many of the properties observed in cells rendered genomically unstable by radiation (Morgan, 2003a, b; see also Section 4.2.1). Genomic instability may be of particular significance in carcinogenesis, because it is a mutator phenotype, as seen in tumours (Bielas *et al.*, 2006). Such perturbation of communication can

lead to the presence in tissue of cells that have lost important functions or gained new functions that are inappropriate to their location. One such function would be a selective advantage in growth that may be endowed by the acquisition of mutations to, for example, genes that control the cell cycle, called "gatekeepers", and genes that are thought to stabilize the genome, called "caretakers" (Kinzler & Vogelstein, 1997).

(a) The cancer stem cell concept

More recently, accumulating evidence described a hierarchical organization of tumours by introducing the concept of cancer stem-cells (NB: Cancer stem cells are not to be confused with normal stem cells. They are cancer cells that are able to divide but whose growth is restricted by the surrounding differentiated cells within the tissue.)

Cancer stem cells differ in that they have lost control over their own population size (for a review, see Visvader & Lindeman, 2008). Data to support a cancer stem cell concept for solid tumours have been reported (Al-Hajj *et al.*, 2003; Hemmati *et al.*, 2003; Passegué *et al.*, 2003; Singh *et al.*, 2003; Serakinci *et al.*, 2004).

In the context of the "cancer stem cell" model, normal tissue may contain quiescent foci of cancer stem cells surrounded by non-dividing differentiated cancer cells that limit the further growth of the tumour (Enderling *et al.*, 2009). It has been postulated that removal through a cell-death process such as apoptosis of the differentiated peripheral cells can release the stem-cell population, and lead to further growth of the tumour.

The radiosensitivity of cancer stem cells differs from that of other cell types, and several studies have shown that they are usually more radioresistant (Rachidi *et al.*, 2007; Altaner, 2008; Lomonaco *et al.*, 2009; Woodward & Bristow, 2009).

The overall effect of this complexity is that ionizing radiation, in the context of carcinogenesis, may serve to both initiate new tumours and promote, as well as in some circumstances inhibit, existing subclinical tumours (Woodward & Bristow, 2009). Thus, the tumourigenic effects of radiation are dependent not only on the nature of the energy-deposition process, but also on the properties of the host tissue/organism.

Indeed, some models (Heidenreich *et al.*, 2007; Heidenreich & Paretzke, 2008) propose that radiation can also promote very efficiently tumour progression in particular for organisms such as humans for which senescence is an efficient barrier, and in which "dormant" cells at different stages of tumour progression have been found in an increased number of organs (Corvi *et al.*, 2001).

4.2.7 Host factors

Genetic variation in specific genes including those involved in human radiation-sensitive cancer syndromes such as ataxia-telangiectasia mutated (ATM), and tumour-suppressor genes such as *TP53*; familial inheritance of mutated genes such as breast cancer *BRCA1* and *BRCA2* – involved in the repair of DNA double-strand breaks, and abnormal reactive oxygen species levels due to, e.g. inflammation, might increase the host susceptibility to radiation-induced cancers. In addition, age, the acquisition of sequence mutations, chromosomal damage, modifications of allelic imprinting and telomere dysfunction may modulate the processing efficiency of abnormal phenotypes in the irradiated tissue (IARC, 2000; ICRP, 2005; BEIR VII, 2006; Allan, 2008).

4.3 Mechanism of carcinogenesis of neutrons: an example of ionizing radiation

Because studies of human exposures to neutrons are extremely limited, mechanistic data for this ionizing radiation were given a special emphasis in this chapter.

4.3.1 Specificity of the exposure to neutrons

Neutrons are uniquely a particle radiation with no charge; however they produce charged particles (e.g. protons) through their interactions with atomic nuclei, and are therefore an ionizing radiation.

The densely ionizing particles formed upon interaction of neutrons with atomic nuclei produce a spectrum of molecular damage that overlaps with that induced by sparsely ionizing radiation. However, neutrons are more effective in causing biological damage because they release more of their energy in clusters of ionizing events, giving rise to more severe local damage, including clustered and complex DNA lesions that are not readily repaired. Although neutrons, like X- and γ-rays, produce double-strand breaks, the neutron-induced DNA breaks are repaired much more slowly than those produced by the sparsely ionizing radiation types (Sakai *et al.*, 1987; Peak *et al.*, 1989; Kysela *et al.*, 1993); this is also the case for other high-LET radiation such as α-particles (Goodhead, 1994; Ward, 1995; Gulston *et al.*, 2004; Pearson *et al.*, 2004).

4.3.2 Induction of chromosomal aberrations following exposure to neutrons

(a) Studies in humans

Chromosomal aberrations including rings, dicentrics and acentric fragments were induced in the circulating lymphocytes of eight men exposed during an accident involving the release of γ-radiation and fission neutrons in a nuclear plant. The neutrons contributed about 26% of the total dose. About 16–17 years after the accident, six of the men still had residual chromosomal aberrations (Bender & Gooch, 1963; Goh, 1975; Littlefield & Joiner, 1978). Similar results were reported after critical accidents also involving mixed exposures in Belgium (Jammet *et al.*, 1980), and Serbia and Montenegro, formerly Yugoslavia (Pendic & Djordjevic, 1968; 19-yr follow-up, Pendić *et al.*, 1980).

The same types of chromosomal aberration were found in the lymphocytes of patients exposed during neutron therapy, with 5–15% of contaminating γ-rays (Schmid *et al.*, 1980). Within the limits of the studies mentioned above, the effects were found to be dose-dependent.

An evaluation of the persistence of chromosomal aberrations in patients receiving fractionated neutron therapy to tumours located at various sites showed that neutron-induced dicentrics and rings disappeared from the peripheral circulation within the first 3 years after exposure, while translocations persisted for more than 17 years (Littlefield *et al.*, 2000).

Chromosomal aberrations, micronuclei, and sister chromatid exchange were analysed in the peripheral lymphocytes of 18 British pilots of the supersonic airplane Concorde and ten [non-British] controls (Heimers, 2000). Based on in-flight radiation monitoring, the average total annual dose to aircrew members was estimated to be about 3 mSv. The frequency of dicentric chromosomes was increased 8-fold ($P < 0.05$) in the group of pilots. The frequency of micronuclei was significantly elevated, but that of sister chromatid exchange did not differ from that in the control group. The yield of dicentrics was higher in flight crews on supersonic flights than on subsonic routes, but the difference was not significant. The overdispersion of dicentric chromosomes showed the influence of high-LET cosmic radiation.

(b) Studies in exposed animals

Fission neutrons were reported to induce germ-line mutations in mice, including visible dominant mutations (Batchelor *et al.*, 1966), dominant lethal mutations (Grahn *et al.*, 1979, 1984, 1986), visible recessive mutations (Russell, 1965, 1972), and specific locus mutations (Russell, 1967; Cattanach, 1971). Neutrons have also been shown to induce *Hprt* mutations in splenic lymphocytes of mice (Kataoka *et al.*, 1993). Point mutations in K-*Ras* and N-*Ras* oncogenes were found in malignant tissue from mice exposed to neutrons, but the mutations could not be directly ascribed to the exposure (Zhang & Woloschak, 1998). Sister chromatid exchange was induced in bone-marrow cells of young rats exposed to fission neutrons (Poncy *et al.*, 1988), while micronuclei and chromosomal aberrations were observed in splenocytes of mice exposed to neutrons *in vivo* (Darroudi *et al.*, 1992). Reciprocal translocations were induced in stem-cell spermatogonia of rhesus monkeys exposed to neutrons (van Buul, 1989). In all these experiments, the fission neutrons were many-fold more effective, on the basis of absorbed dose, than sparsely ionizing radiation.

(c) Studies in cultured cells

DNA breaks induced by fast neutrons in L5178Y mouse lymphoma cells were classified into three types on the basis of their repair profiles: rapidly repaired breaks (half-time, 3–5 minutes), slowly repaired breaks (half-time, 70 minutes), and non-repaired breaks. Neutrons induced less of the rapidly repaired damage, a nearly equal amount of slowly repaired damage, and more non-repaired damage when compared with equal doses of X- or γ-radiation (Sakai *et al.*, 1987).

In mammalian cells, neutrons were more efficient than the same absorbed dose of X-rays or γ-rays at inducing gene mutation and chromosomal aberrations (Fabry *et al.*, 1985; Roberts & Holt, 1985; Hei *et al.*, 1988; Nakamura & Sawada, 1988; Kronenberg & Little, 1989; Kronenberg, 1991), and transformation (Balcer-Kubiczek *et al.*, 1988: Miller *et al.*, 1989; Komatsu *et al.*, 1993). In addition, extensive measurements of the induction of chromosomal aberrations (dicentrics or dicentric plus centric rings) in human lymphocytes as a function of the neutron energy have been performed (Lloyd *et al.*, 1976; Sevan'kaev *et al.*, 1979; Edwards, 1999; Schmid *et al.*, 2003).

4.4 Synthesis

- The energy-deposition characteristics of all sources of ionizing radiation are relatively well understood.
- All types of ionizing radiation, including neutron radiation, transfer their energy to biological material in clusters of ionization and excitation events, primarily through a free-electron-mediated mechanism.
- In cells, energy deposition from all types of ionizing radiation results in a wide variety of molecular damage; in DNA, this includes base damage and single- and double-strand breaks, some of which may be clustered and form complex lesions. Subsequent processing of these lesions may lead to chromosomal aberrations and mutations.
- Much evidence points to damage to DNA being of primary importance in the biological outcome of exposure to ionizing radiation, particularly the loss of cellular ability to form clones. It is generally assumed that the same DNA damage leads to tumorigenesis, and there is some evidence to support this.
- How the cell processes the initially produced damage to DNA to yield tumours is unknown; although many hypotheses have been the subject of research, few have gained wide consensus.

- Genome-wide sequencing of tumours has shown wide heterogeneity in constituent mutations, indicating there may be multiple pathways to tumour formation.
- Tumours produced after exposure to ionizing radiation have not been shown to carry any characteristic molecular markers.
- There is emerging consensus that epigenetic factors are important in tumorigenic processes. Notably, radiation induces effects such as genomic instability and bystander effects, which are epigenetic in origin.
- Also important are the interactions at the tissue level between radiation-damaged cells and normal cells, which may serve to modulate the effects of radiation. In addition, host factors such as age, gender, changes in immune status, telomere dysfunction, and genetic variations in specific genes may play a role, as well as modulation of gene expression.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of X-radiation and of γ-radiation. X-radiation and γ-radiation cause cancer of the salivary gland, oesophagus, stomach, colon, lung, bone, basal cell of the skin, female breast, kidney, urinary bladder, brain and CNS, thyroid, and leukaemia (excluding chronic lymphocytic leukaemia). Also, positive associations have been observed between X-radiation and γ-radiation and cancer of the rectum, liver, pancreas, ovary, and prostate, and non-Hodgkin lymphoma and multiple myeloma.

In-utero exposure to X-radiation and γ-radiation causes cancer.

There is *sufficient evidence* in experimental animals for the carcinogenicity of X-radiation and of γ-radiation.

X-radiation and γ-radiation are *carcinogenic to humans (Group 1).*

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NEUTRON RADIATION

Neutrons were considered by a previous IARC Working Group in 1999 (IARC, 2000). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

See Section 1 of the *Monograph* on X-radiation and γ-radiation in this volume.

2. Cancer in Humans

Studies of human exposures to neutron radiation are extremely limited. The major group is the atomic bomb (A-bomb) survivors who were exposed to fission neutrons. Based upon the latest A-bomb dose reconstruction for Hiroshima and Nagasaki, neutron radiation accounted for about at most 1% of the total absorbed radiation dose (Preston *et al.*, 2004). The neutron component was even less for those in Nagasaki, in which the bomb was plutonium-based in contrast to the uranium weapon used in Hiroshima. Using experimental data, it is assumed that the relative biological effectiveness (RBE) of the A-bomb neutrons is 10 times that of the γ-radiation (Preston *et al.*, 2004). It has been suggested that this value is too low, and thus the neutron component could account for a greater fraction of the total effective dose in the Hiroshima cohort (Kellerer & Walsh, 2001; Kellerer *et al.*, 2002, 2006; Sasaki *et al.*, 2006, 2008; Schneider & Walsh, 2008). This in turn would reduce the estimated cancer risk of γ-radiation exposures. For example, Kellerer & Walsh (2001) and Kellerer *et al.* (2002) used values of the RBE in the range of 20–50 for the evaluation of risks for solid cancer from γ-radiation exposure. Although there are city differences, the neutron component of dose is too small to make conclusions about neutron effects and RBE estimates (Kellerer & Walsh, 2001; Preston *et al.*, 2004).

Nuclear workers are occasionally exposed to neutrons, but their numbers are small, and they typically will also be exposed to higher doses of γ-radiation. Several studies have been carried out on airline crews because of their exposure to neutrons from cosmic rays during high-altitude flights. It is estimated that more than 50% of the effective dose is from high linear-energy-transfer (LET) radiation, most of which is neutron (Goldhagen, 2000), and the estimated total radiation exposure is in the range of 0.2–9.1 mSv per year, well below occupational limits of 20 mSv per year (Wilson, 2000). Increases in breast cancer and melanoma have been observed, but not leukaemia. Also, confounding factors include circadian rhythm disruption, which may increase the risk of endocrine tumours, as well as UV exposures and the risk for melanoma. Sigurdson & Ron (2004) summarize well the

studies and issues, and there is not a clear cause and effect relationship between any site-specific cancer risk and employment as a pilot or flight attendant.

Studies of patients treated with neutrons are limited and difficult to evaluate due to the small numbers of survivors and the complex dosimetry often combined with X-rays and chemotherapy agents. Recently, MacDougall *et al.* (2006) conducted a review of long-term follow-up sites in Scotland, the United Kingdom, of fast-neutron therapy for various cancers among 620 patients. Three cases of sarcomas were reported, which was 111 times the expected in the Scottish population. A study in the United States of America on 484 cancer patients who received neutron therapy reported poor patient survival; only 5% of cases survived 10 years or more (Sigurdson *et al.*, 2002). Nearly 50% of the study patients were treated for cancer of the uterine cervix, prostate, or head and neck.

3. Cancer in Experimental Animals

3.1 Previous *IARC Monograph*

Like X-and γ-radiation, neutrons are classified as ionizing radiation. The rationale for most studies of cancer in animals on neutrons have been to quantitatively compare neutron and X- or γ-ray effects as a function of dose to obtain a measure of the RBE for the purpose of weighting risks from neutron exposures compared with those for X- or γ-rays. The following text summarizes the studies reviewed in the previous *IARC Monograph* (IARC, 2000).

Neutrons have been tested at various doses and dose rates with wide ranges of mean energy from various sources (reactors, ^{252}Cf, ^{235}U) for carcinogenicity in mice, rats, rabbits, dogs, and rhesus monkeys. Fission-spectrum neutrons were used in most of these studies.

In mice, neutrons clearly increased the incidence in:

- myeloid leukaemia and malignant lymphoma including thymic lymphoma (Upton *et al.*, 1970; Ullrich *et al.*, 1976; Ullrich & Preston, 1987; Covelli *et al.*, 1989; Seyama *et al.*, 1991; Grahn *et al.*, 1992; Ito *et al.*, 1992; Takahashi *et al.*, 1992; Di Majo *et al.*, 1994, 1996; Storer & Fry, 1995)
- benign and malignant tumours (e.g. adenocarcinomas) of the lung and the mammary gland (Ullrich *et al.*, 1976, 1977; Ullrich & Storer, 1979a, b; Ullrich, 1983; Coggle, 1988; Seyama *et al.*, 1991; Grahn *et al.*, 1992; Di Majo *et al.*, 1994, 1996; Storer & Fry, 1995)
- benign and malignant tumours of the ovary (Ullrich *et al.*, 1976, 1977; Ullrich, 1983; Seyama *et al.*, 1991; Grahn *et al.*, 1992; Ito *et al.*, 1992; Takahashi *et al.*, 1992; Storer & Fry, 1995; Di Majo *et al.*, 1996)
- benign and malignant tumours of the liver (Di Majo *et al.*, 1990, 1994, 1996; Seyama *et al.*, 1991; Grahn *et al.*, 1992; Ito *et al.*, 1992; Takahashi *et al.*, 1992; Storer & Fry, 1995; Watanabe *et al.*, 1996)
- benign and malignant tumours of the Harderian gland (Seyama *et al.*, 1991; Grahn *et al.*, 1992; Di Majo *et al.*, 1996)
- tumours of the pituitary and adrenal gland (Seyama *et al.*, 1991; Ito *et al.*, 1992; Takahashi *et al.*, 1992).

Neutrons also induced lipomas (Seyama *et al.*, 1991), squamous cell carcinomas of the skin (Di Majo *et al.*, 1994), subcutaneous fibrosarcomas and osteosarcomas (Storer & Fry, 1995).

In rats, neutrons clearly increased the incidence in malignant mammary tumours (Vogel & Zaldívar, 1972; Shellabarger, 1976; Montour *et al.*, 1977; Broerse *et al.*, 1986, 1987) and lung carcinomas (Chmelevsky *et al.*, 1984; Lafuma

et al., 1989). Neutrons also induced benign and malignant liver tumours (Spiethoff *et al.*, 1992).

In rabbits, neutrons induced subcutaneous fibrosarcomas and basal cell tumours of the skin (Hulse, 1980).

Neutrons were also tested for carcinogenicity in mice exposed prenatally, and in mice after male parental exposure. In adult animals, the incidences of leukaemia and of ovarian, mammary, lung and liver tumours were increased in a dose-related manner, although the incidence often decreased at high doses. Prenatal and parental exposure of mice resulted in increased incidences of liver tumours in the offspring (IARC, 2000).

While a γ-ray component was present in the exposure in most studies, it was generally small, and the carcinogenic effects observed could clearly be attributed to the neutrons. Enhancement of tumour incidence was often observed with high doses at a 1ow dose rate. In virtually all studies, neutrons were more effective in inducing tumours than were X-radiation or γ-radiation when compared on the basis of absorbed dose (IARC, 2000).

Only additional data since the previous *IARC Monograph* will be discussed in the following Section (see also Table 3.1). The majority of these were reanalyses of historical data.

3.2 Carcinogenicity in adult animals

Studies in adult animals have focused on effects as a function of dose, dose rate or fractionation, and neutron energy.

3.2.1 Mouse

Two studies present reanalyses of previously published data.

The first of these summarized a series of studies conducted over several years comparing neutron and X-radiation effects. Experiments in mice examining carcinogenic effects of single doses of 1.5 MeV neutrons were compared with 250 kVp X-rays, and effects of fractionation were also described. While the sample sizes were small, the studies provide clear evidence for the carcinogenic effects of both fission-spectrum and monoenergetic 1.5 MeV neutrons at doses as low as 100 mGy (Di Majo *et al.*, 2003).

The second was an analysis of historical data for lung cancer risk derived from a large series of studies conducted at Argonne National Laboratory in 15957 mice with acute and fractionated exposures to γ-rays or fission-spectrum neutrons (Heidenreich *et al.*, 2006). This analysis reported that at low doses neutrons are approximately 10 times more effective than γ-rays with respect to the induction of lung tumours.

Watanabe *et al.* (2007) examined tumour induction in mice of both sexes following irradiation at a dose of 500 mGy with monoenergetic neutrons of various energies (0.18, 0.32, 0.6, and 1.0 MeV). No comparisons were made with X- or γ-rays. These studies demonstrated a substantial and significant increase in the incidence of tumours, mainly hepatocellular carcinoma, following neutron irradiation, with no apparent differences among the different neutron energies. Lung, ovary and Harderian gland tumour incidence was also increased.

3.2.2 Rat

Wolf *et al.* (2000) examined the effectiveness of fission-spectrum neutrons compared to X- and γ-rays for the induction of a variety of tumours with a high degree of lethality in Sprague-Dawley female rats from historical data. Analysis indicated that at doses of 20 mGy, neutrons were approximately 50 times more effective than γ-rays with respect to inducing carcinogenicity.

3.2.3 Rhesus monkey

Two reports on the same cohort of monkeys irradiated with whole-body doses of either X-rays or fission-spectrum neutrons were published by

Table 3.1 Studies in experimental animals exposed to neutrons since IARC (2000)

Species, strain, sex Duration Reference	Dosing regiment Animals/group at start	Incidence of tumours	Significance
Mouse, B6C3F$_1$, CBA (M, F) Duration (NR) Di Majo *et al.* (2003)	Fission neutrons: M–3 mo-old, received total doses of 0, 25, 50, 100 and 170 mGy delivered in 5 daily fractions or a single dose of 170 mGy F–1 mo-old, received 1.5 Mev neutrons at single doses (0, 5, 10, 20, 40, 80, 160 mGy) Number of animals at start (NR)	3 mo-old males B6C3F$_1$ fractionated Dose–AML, solid tumours (%): 0–0, 16.4 25–0, 20.1 50–0, 17.2 100–0, *26.0 170–2.7, *28.8 Single dose: 170–2.2, *30.4	*$P \leq 0.05$
		1 mo-old females B6C3F$_1$ Dose–solid tumours, ovarian tumours (%): 0–47.9, 17.2 5–40.5, 23.3 10–44.4, 18.1 20–43.6, 18.1 40–44.6, 19.6 80–58.9, 21.1 160–66.7, 33.3	
	M and F received 0, 100 mGy	CBA male Dose–lymphoma, AML, solid tumours (%): 0–4.0, 0, 58.0 10–10.1, 3.8, 77.2 CBA females Dose–lymphoma, solid tumours, ovarian tumours (%): 0–10.3, 41.4, 20.7 10–20.0, 50.0, 10.0	

Table 3.1 (continued)

Species, strain, sex Duration Reference	Dosing regiment Animals/group at start	Incidence of tumours	Significance
Mouse, B6CF$_1$ (M, F), Duration (NR) Heidenreich *et al.* (2006)	Acute and fractionated fission neutrons doses, range 10–1500 mGy 15 957 animals	Tumour of the lung: M: RBE for lifetime = 10 For acute neutron vs acute gamma exposures For fractionated neutrons RBE = 4	
Mouse, Crj:B6C3F$_1$ (M, F) 13 mo Watanabe *et al.* (2007)	Single doses of 500 mGy of monoenergetic neutrons at energies of 0.18, 0.32, 0.6 and 1.0 MeV 30/group	Dose–tumours of the liver and lung (%): M– 0–11.0, 0.0 0.18–33.0, 13.0 0.32–31.0, 12.0 0.6–40.0, 7.0 1.0–17.0, 7.0 Dose–tumours of the ovary, liver, lung, and Harderian gland (%): F– 0.0–0.0, 0.0, 0.0, 0.0 0.18–68.0, 14.0, 4.0, 7.0 0.32–67.0, 4.0, 7.0, 11.0 0.6–54.0, 14.0, 11.0, 25.0 1.0–56.0, 26.0, 4.0, 22.0	$P < 0.05$ irradiated vs control $P < 0.05$ irradiated vs control
Rat, Sprague-Dawley Age at start (NS) Lifespan Wolf *et al.* (2000)	Fission neutrons at dose of 12, 20, 60, 100, 320 mGy 70–150; 795 controls	ERR: 0.0–0 12–1.0 20–2.0 60–6 100–8 320–12	

Table 3.1 (continued)

Species, strain, sex Duration Reference	Dosing regiment Animals/group at start	Incidence of tumours	Significance
Rhesus monkey Lifespan Broerse *et al.* (2000) and Hollander *et al.* (2003)	Fission neutrons at doses from 2300 to 4400 with a mean of 3400 mGy 9, 21 controls	Malignant tumours: Controls–30% Neutrons–90% Mean absolute age (yr): Controls–28.4 Neutrons–14.9	
Mouse, $BC3F_1$ (M, F) Di Majo *et al.* (2003)	Fission neutrons at a dose of 90 mGy at 17-d post conception	Dose–AML, solid tumours (%): M– 0.0–0, 25.0 90–2.0, 42.9 Dose–solid tumours, ovarian tumours (%): F– 0.0–37.1, 8.6 90–52.4, 14.3	

AML, acute myeloid leukaemia; ERR, excess relative risk; F, female; M, male; mo, month or months; NR, not reported; NS, not significant; RBE, relative biological effect; vs, versus

Broerse *et al.* (2000) and by Hollander *et al.* (2003). A total of 20 monkeys were irradiated with X-rays at doses in the range of 2800–8600 mGy, and nine monkeys with fission-spectrum neutrons at doses of 2300–4400 mGy. Controls consisted of 21 age-matched non-irradiated rhesus monkeys. Both types of radiations increased the frequency of a variety of malignant tumours, and decreased their latency compared with non-irradiated controls. In particular, an increase in the incidence of kidney cortical carcinoma was observed (4/9 versus 0/21 controls). Neutrons appeared to be more effective with 90% (8/9) of the neutron-irradiated animals dying with tumours compared to 50% (10/20) following X-ray irradiation and 30% (7/21) in controls.

3.3 Prenatal exposure

3.3.1 Mouse

Effects of irradiation of male and female mice at 17 days post conception with a 90 mGy dose of fission-spectrum neutrons or a 300 mGy dose of X-rays were reported by Di Majo *et al.* (2003). While the numbers of animals were small (n = 35–42), a small but significant increase in total solid tumours as well as ovarian tumours in female mice was observed after the 90 mGy neutron dose.

3.4 Synthesis

Although the number of studies conducted examining the tumorigenic effects of neutrons since 2000 is small, they support and confirm the conclusions of the previous *IARC Monograph*. Neutron radiation has clear carcinogenic effects in a variety of experimental animal studies in mice, rats and monkeys. In addition, neutron irradiation is more effective with respect to its carcinogenic actions than are X- or γ-rays. There is also evidence of an increased incidence of tumours as a function of dose in several studies in mice and one new study in rats.

4. Other Relevant Data

See Section 4 of the *Monograph* on X-radiation and γ-radiation in this volume.

5. Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of neutron radiation.

There is *sufficient evidence* in experimental animals for the carcinogenicity of neutron radiation.

Neutron radiation is *carcinogenic to humans (Group 1)*.

In making the overall evaluation, the Working Group took into consideration the following:

- Every relevant biological effect of X- or γ-radiation that has been examined has been found to be induced by neutrons, including neoplastic cell transformation, mutations *in vitro*, germ-cell mutations *in vivo*, chromosomal aberrations *in vivo* and *in vitro*, and cancer in experimental animals.
- Structural chromosomal aberrations (including rings, dicentrics and acentric fragments) and numerical chromosomal aberrations are induced in the lymphocytes of people exposed to neutrons.

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INTERNALIZED α-PARTICLE EMITTING RADIONUCLIDES

Internalized radionuclides that emit α-particles were considered by a previous IARC Working Group in 2000 (IARC, 2001). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

See Section 1 of the *Monograph* on X-radiation and γ-radiation in this volume.

2. Cancer in Humans

2.1 Radon

Radon is a natural radioactive gas produced by the decay of uranium and thorium, which are present in all rocks and soils in small quantities. There are several isotopes of radon, the most important of which are ^{222}Rn (produced from ^{238}U) and ^{220}Rn (produced from thorium). ^{220}Rn is also known as thoron because of its parent radionuclide. In the United Kingdom, it has been shown that ^{220}Rn delivers much smaller doses to the public in indoor environments than ^{222}Rn (The Independent Advisory Group on Ionising Radiation, 2009). Unlike ^{222}Rn, ^{220}Rn is not formed during the radioactive decay of ^{238}U, and is hence not present at appreciable levels in uranium mines.

The epidemiological evidence on the cancer risks from radon is derived largely from cohort studies of underground miners that had been exposed to high levels of radon in the past. More recently, a series of case–control studies of lower exposures to residential radon have also been conducted.

The previous *IARC Monograph* on radon IARC (1988) states that radon is a cause of lung cancer in humans, based on clear excess lung cancer rates consistently observed in underground miners, and elevated lung cancer risks seen in experimental animals exposed to radon. In a subsequent evaluation by IARC (2001), additional epidemiological evidence of an increased lung cancer was also seen in case–control studies of residential radon. Although results from the 13 case–control studies available at that time were not conclusive, the Working Group noted that the risk estimates from a meta-analyses of eight such studies were consistent with estimates based on the underground miner data (Lubin & Boice, 1997).

In a detailed evaluation of the health risks of radon by the Committee on the Biological Effects of Ionizing Radiation (BEIR) within the

US National Research Council (BEIR IV, 1988), it was also reported that radon is a cause of lung cancer in humans. An important aspect of this work was the development of risk projection models for radon-related lung cancer, which provides estimates of the lung cancer risk associated with residential radon, depending on age, time since exposure, and either concentration or duration of exposure.

In an effort to synthesize the main epidemiological findings and assist in the evaluation of the lung cancer risks associated with occupational and environmental exposure to radon, several combined analyses of the primary raw data from studies of radon and lung cancer have been conducted. Several combined analyses of epidemiological data from 11 cohorts of underground miners have been conducted (BEIR IV, 1988; Lubin *et al.*, 1994; Lubin & Boice, 1997; BEIR VI, 1999). Howe (2006) conducted a combined analysis of data from three cohorts of uranium miners from Canada, and Tomášek *et al.* (2008) conducted a combined analysis of Czech and French uranium miners. Combined analyses of epidemiological data from seven North American case–control studies of residential radon and lung cancer (Krewski *et al.*, 2005), 13 European studies (Darby *et al.*, 2005, 2006), and two studies from the People's Republic of China (Lubin *et al.*, 2004) have also been conducted.

Cancers other than lung cancer, notably haematopoietic lesions, have been investigated in some of the cohort studies of miners. Case–control studies of residential radon and childhood cancers, including leukaemia, have also been conducted. Ecological studies of environmental radon and the risk of lung and other cancers have been reported, but these are less informative than the cohort and case–control studies discussed previously (IARC, 2001).

2.1.1 Occupational studies of underground miners

(a) Early observations of lung disease in miners

Underground mining was the first occupation associated with an increased risk of lung cancer. Metal ores were mined in the Erz mountains (a range between Bohemia and Saxony), in Schneeberg from the 1400s and in Joachimsthal (Jachymov) from the 1500s. As early as the 16th century, Georg Agricola, in his treatise 'De re Metallica', described exceptionally high mortality rates from respiratory diseases among miners in the Erz mountains. The disease in miners was recognized as cancer in 1879 by Harting & Hesse (1879). This report provided clinical and autopsy descriptions of intrathoracic neoplasms in miners, which were classified as lymphosarcoma. During the early 20th century, histopathological review of a series of cases established that the malignancy prevalent among miners in the Erz mountains was primary cancer of the lung (Arnstein, 1913; Rostocki, 1926). Many authors offered explanations for this excess including exposures to dusts or metals in the ore (particularly arsenic). In 1932, Pirchan and Sikl suggested that radioactivity was the most probable cause of the cancers observed in Jachymov (Pirchan & Sikl, 1932).

(b) Cohort studies

The first epidemiological evidence of an increased lung cancer risk among underground miners exposed to radon in the Colorado Plateau was given by Archer *et al.* (1962). Subsequent analyses of this cohort were conducted by Wagoner *et al.* (1964, 1965) as additional lung cancer cases accrued; the latter analysis was the first to relate lung cancer risk to cumulative exposure to radon progeny in terms of working-level months (WLM). Stram *et al.* (1999) conducted detailed analyses of the effects of uncertainties in radon exposures within this cohort on radon-related lung cancer risk estimates. Another early study reported

lung cancer risk in Canadian fluorspar mines in Newfoundland, where substantial amounts of water seeping through the mines contain radon gas (de Villiers, 1966). The first statistical study on the incidence of lung cancer among uranium miners from former Czechoslovakia (the Czech Republic) was published in 1966 by (Rericha *et al.*, 1966), followed by results on autopsy-verified lung cancer cases (Horacek, 1968). The first epidemiological study in uranium miners from former Czechoslovakia (the Czech Republic) was initiated in the late 1960s, with first results reported shortly thereafter (Sevc *et al.*, 1971). In contrast to other epidemiological studies, there were hundreds of radon measurements per year in every mine. As of now, cancer risks in 19 cohorts of underground miners exposed to radon have been investigated (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.1.pdf). In each of these cohorts, occupational exposure to radon decay products was associated with increased lung cancer risk.

To increase statistical power, particularly in quantifying the modifying effect of different factors related to time or age, attempts were made to pool individual data from related studies for the joint estimation of risk and the evaluation of modifying factors. The first such analyses were conducted by the BEIR IV committee (BEIR IV, 1988), and included a combined analysis of three studies of uranium miners in the Colorado Plateau, USA, the Eldorado mine in Ontario, Canada, and Swedish iron miners in Malmberget.

By building on initial work by Lubin *et al.* (1994, 1995) and Lubin & Boice (1997), a subsequent report by the US National Research Council (Lubin, 2003) extended the combined analysis to encompass 11 cohorts of underground miners (see Table 2.1 on-line). An important aspect of this analysis was the development of a comprehensive risk model for radon-induced lung cancer in underground miners taking into account age, time since exposure, and either exposure concentration or duration of exposure (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.2.pdf). The previous risk model developed by the BEIR IV committee did not consider exposure concentration or duration. The BEIR VI risk models indicated that lung cancer risk decreased with time since exposure and age; for a fixed cumulative exposure, the risk decreased with increasing exposure concentration (reflecting an inverse exposure–rate effect), and increased with duration of exposure.

Another pooled analysis was conducted in a joint cohort of Czech and French uranium miners, including a total of 10100 miners and 574 lung cancers (Tomášek *et al.*, 2008). Cohort members were subject to relatively low levels of radon exposure (mostly below 4 working-level (WL)); exposure measurements were available for over 96% of the total exposure time experienced by individuals in this joint cohort. The effect of the quality of the exposure data in this joint study was analysed by distinguishing exposures based on measurements from those that were estimated or extrapolated. If exposure quality is not accounted for, the estimated ERR/WLM is substantially underestimated by a factor of 3.4 in the French study; however, effect modification by exposure quality was not observed in this study with relatively low annual exposures, for which measurements were almost always available. The term ERR/WLM quantifies the increased in risk per exposure in working-level months. More specifically, WLM is a time-integrated exposure measure, and it is the product of the time in working months (170 hours) and working-level. One WL equals any combination of radon progeny in 1 litre of air that gives the ultimate emission of 130000 MeV of energy of α-particles. Consequently, 1 WLM corresponds to 2.08×10^{-5} J/m^3 x 170 hours = 3.5×10^{-3} J-hours/m^3.

Predictions of lung cancer risk were not substantially different from those based on the BEIR VI risk models (Table 2.2 on-line). [The

Working Group noted that a complicating factor in the interpretation of data on lung cancer risks among uranium miners from former Czechoslovakia (the Czech Republic) is the joint exposure to γ-radiation, which can also increase lung cancer risk.]

In contrast to the empirical radon risk projection models developed by the BEIR IV committee, the BEIR VI committee (BEIR VI, 1999) applied biologically based risk models to describe the lung cancer risks relation to radon in the Czech and French cohorts; a discussion on the interpretation of risk projections derived from the application of such models to epidemiological data on radon is provided in Heidenreich & Paretzke (2004).

Grosche *et al.* (2006) reported on a new German cohort of 59000 uranium miners, with 2388 lung cancer cases. This is the largest of the miner cohorts investigated to date, and is comparable in size to the 11 cohorts considered in the BEIR VI report combined (BEIR VI, 1999). Patterns of risk based on age and exposure concentration were similar to those found in the BEIR VI report (BEIR VI, 1999), although the effect of time since exposure was somewhat different (Table 2.2 on-line), possibly reflecting the higher proportion of missing causes of death in the early years of follow-up. Howe (2006) conducted a combined analysis of Canadian data on uranium miners from the Beaverlodge, Port Radium, and Port Hope cohorts. The study included 17660 workers, with 618 cases of lung cancer. Patterns of lung cancer risk were similar to those found in the BEIR VI report (Table 2.2 on-line).

(c) *Joint effects of radon and smoking on lung cancer risk*

Because tobacco smoking is a powerful risk factor for lung cancer, the joint effects of radon and smoking need to be considered. The interactions between exposure to radon and smoking in the six studies of miners for which smoking information was available were investigated by Lubin *et al.* (1995). Although some studies were consistent with additive effects of radon and tobacco smoke on lung cancer risk, other interactions between radon and tobacco smoke in which the joint effects of these two agents were greater than additive (Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.3.pdf). Six of the above studies were jointly analysed in the BEIR VI report (BEIR VI, 1999), which suggested a submultiplicative model. The ratio of ERR/WLM in non-smokers and smokers was 3.0 (95%CI: 0.3 – 29.2). [The Working Group noted that the confidence interval of this ratio was relatively wide, because of the small numbers of lung cancers (64) among non-smokers.] In these studies, the radon risk coefficients adjusted for smoking were not substantially different from those obtained when smoking was ignored.

(d) *Lung cancer risks among haematite miners*

Previous *IARC Monographs* have implicated radon as contributing to the excess lung cancer risk observed in haematite miners (IARC, 1972, 1987, 1988). Volume 43 of the *IARC Monographs* (IARC, 1988) states that "underground haematite mining with exposure to radon is carcinogenic to humans." Lawler *et al.* (1985) noted no increased mortality in 10403 lung cancer among miners in Minnesota haematite mines relative to population rates (SMR, 1.00) with low-grade exposure to radon daughters and silica dust. Kinlen & Willows (1988) noted that other iron mines, like that in Cumbria in the United Kingdom, in which 864 underground miners were studied, the SMR for lung cancer among workers was increased relative to population rates in the period 1948–67 (SMR, 1.53), but not thereafter (SMR, 1.13). Radon levels in early periods were in the range of 0.35–3.2 WL, and decreased to

0.1–0.8 WL, suggesting that radon was the causative agent. In a study of 5406 haematite miners in China, a significant excess of lung cancer (SMR, 3.7) was observed, although this was based on only 29 cases of lung cancer (Chen *et al.*, 1990). In this study, lung cancer risk increased notably with increasing radon concentrations and with increasing dust concentrations; however, the authors were unable to evaluate the independent effects of radon and dust, because these two hazards were positively correlated. Collectively, these observations provide evidence that radon increases the risk of lung cancer in haematite miners.

(e) Leukaemia risks in miners

Health effects of exposure to radon progeny other than lung cancer, including leukaemia, have been addressed in several miner studies (see Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.4.pdf). A combined analysis of 11 cohorts of underground miners showed no evidence of an increased risk of leukaemia (Darby, 1995). However, significant trends in the risk of leukaemia were found in the Czech study in relation to duration of exposure (Tomášek *et al.*, 1993; Tomášek & Zárská, 2004), and to cumulative joint exposure to radiation from radon gas, external sources of exposure to γ-radiation, and long-lived radionuclides (Tomášek & Kubik, 2006). In a separate Czech cohort, the risk of leukaemia also increased with cumulative radon exposure (Rericha *et al.*, 2006). Another analysis of a large German cohort of uranium miners has shown a significant increase in the incidence of leukaemia among the highest exposed miners (Möhner *et al.*, 2006), although leukaemia mortality was not associated with exposure to radon progeny (Kreuzer *et al.*, 2008).

(f) Cancers other than lung and leukaemia

Darby *et al.* (2005) found no evidence of an increased risk of other cancers in their pooled analysis of 11 miner cohort studies. In an analysis of the large German cohort, Kreuzer *et al.* (2008) found a statistically significant relationship between cumulative radon exposure and mortality from all extra pulmonary cancers combined; this result persisted after adjustment for potential confounding by arsenic, dust, long-lived radionuclides and γ-radiation. Increasing trends in cancer risk were also reported at several specific sites in this study; however, none of these trends was significant after adjustment for potential confounding.

Sevcová (1989) reported that the risk of basal cell carcinoma among Czech uranium miners was 2–12 times higher than in the general male population. The mean equivalent dose in the basal layer of epidermis was estimated to be 0.6–5.0 Sv, depending on the duration of exposure (Sevcová *et al.*, 1978). Based on 27 cases observed during a 20-year follow-up period, the ERR/Sv was estimated to be 2.2 (Sevcová, 1989).

2.1.2 Environmental studies of indoor radon

An extensive set of case–control studies of indoor radon and lung cancer were designed, and, taken individually, these studies did not provide conclusive evidence of an association between indoor radon exposure and lung cancer risk. Because of the difficulty in identifying the comparatively small relative risks that would be anticipated from indoor radon exposure, combined analyses of these studies were undertaken in North America, Europe and China (see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.5.pdf). The combined analyses had inclusion criteria for each study with clear rules for the selection of persons with lung cancer that included the following: the selection of controls

so as to be representative of the population from which the lung cancer cases arose; the availability of detailed residential histories, compiled in a similar way both for cases and controls; the availability of long-term (minimum 2 months) measurements of radon gas concentrations; and availability of data on smoking habits for individual study subjects.

(a) Combined analysis of North American case–control studies

The combined analysis of seven North American case–control studies included a total of 3662 cases and 4966 controls (Krewski *et al.*, 2005, 2006). All studies used long-term α-particle track detectors to measure the concentration of radon progeny in indoor air for 12 months (Field *et al.*, 2006). Contemporaneous measurements were made in homes that subjects had occupied or were currently occupying; these measurements were used to estimate historical radon concentrations in those homes. Detectors were placed in the living areas and bedroom areas of the home in which subjects had spent the majority of their time. Conditional likelihood regression was used to estimate the excess risk of lung cancer. Table 2.6 (available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.6.pdf) shows the estimated odds ratios for lung cancer by different concentration levels of radon, and the excess odds ratios per 100 Bq/m^3. Odds ratios for lung cancer increased with residential radon concentration. The estimated odds ratio after exposure to radon at a concentration of 100 Bq/m^3 in the exposure time window of 5–30 years before the index date was 1.11 (95%CI: 1.00–1.28). This estimate is compatible with the estimate of 1.12 (95%CI: 1.02–1.25) predicted by downward extrapolation of the miner data.

The examination of potential effect modification by demographic factors (sex, age, education level, respondent type) and smoking variables (smoking status, number of cigarettes per day, duration of smoking, years since quitting smoking) showed no evidence of heterogeneity of radon effects. There was no apparent heterogeneity in the association by sex, educational level, type of respondent (proxy or self), or cigarette smoking, although there was some evidence of a decreasing radon-associated lung cancer risk with age ($P = 0.23$).

Analysis of the effects of radon exposure by different histological types of lung cancer showed the largest excess odds ratio (0.23 per 100 Bq/m^3) for small cell carcinoma, although the confidence limits overlapped with other histological types of lung cancer. Because of the reduced number of subjects, all of the confidence limits for the excess odds ratios for specific histological types of lung cancer included zero. Analyses restricted to subsets of the data with presumed more accurate radon dosimetry (increasing number of years in the 5–30 exposure time window and limiting the number of residences by subjects) resulted in increased estimates of risk with increasing number of years monitored. In addition, excess odds ratios were larger when data were restricted to subjects living in one or two houses compared with no housing restrictions. These results provide direct evidence of an association between residential radon exposure and lung cancer risk.

(b) Combined analysis of the European case–control studies

Combined analysis of case–control studies of indoor radon have also been carried out in Europe. Darby *et al.* (2005, 2006) pooled individual data from all studies and organized them into a uniform data format to more precisely estimate the increased risk of lung cancer due to residential radon exposure, and to determine the modifying effects of smoking, age, sex, and other factors.

Data on smoking history and also on radon exposure history, based on long-term measurements of radon gas concentrations, were available for a total of 7148 persons with lung cancer

and 14208 controls. Among the people with lung cancer, the mean time-weighted observed average residential radon concentration during the 30-year period ending 5 years before diagnosis was 104 Bq/m^3. The ratio of the number of controls to the number of cases differed between the different studies, and the time-weighted average observed residential radon concentration for the controls, with weights proportional to the study-specific numbers of cases, was 97 Bq/m^3. The association between the risk of developing lung cancer and residential radon concentrations in these data was studied using linear models for the relative risk, with stratification for study, age, sex, region of residence within each study, and detailed smoking history. Analyses were carried out first in relation to the observed radon concentration without making any adjustment for the effect of uncertainties in the assessment. The major analyses were then repeated with an approximate adjustment to take into account uncertainties in radon concentrations.

This combined analysis showed that there was clear evidence (P = 0.0007) of an association between the residential radon concentration during the previous 35 years and the risk of lung cancer. The dose–response relationship was linear, and the estimated ERR of lung cancer was 0.08 (95%CI: 0.03–0.16) for a 100 Bq/m^3 increase in the time-weighted average observed radon concentration. This corresponds to an increase of 0.16 (95%CI: 0.05–0.31) per 100 Bq/m^3 increase in usual radon; that is, after correction for the dilution caused by random uncertainties in measuring radon concentrations. The proportionate excess risk did not differ significantly with study, age, sex, or smoking. The dose–response relationship seemed to be linear with no threshold, and remained significant (P = 0.04) in analyses limited to individuals from homes with measured radon concentrations < 200 Bq/m^3. There was no evidence that the dose–response relationship varied between the different studies (P = 0.94), nor were the results dominated by any individual study.

Analysis of radon effects by histological types of lung cancer showed a stronger and statistically significant dose–response relationship with small cell cancer. For squamous cell carcinoma, the estimated value of β was slightly negative, while for adenocarcinoma and for other confirmed histological types, it was positive. However, in all these later three groups the 95% confidence interval for β included zero. [The Working Group noted that not all studies contributed to this analysis.]

Correction for the effects of random uncertainties in the assessment of radon concentrations were made using data on repeat radon measurements in the same home. These corrections resulted in the relative risk per 100 Bq/m^3 nearly doubling from 0.084 to 0.16, with the width of the associated 95% confidence interval increasing from 0.030–0.158 to 0.05–0.31 (Krewski *et al.*, 2005). [The Working Group noted that a similar effect was seen in the North American studies when combined analyses were restricted to data for which the most complete radon dosimetry was available.]

(c) Combined analysis of studies in China

Data from the two studies of residential radon representing two large radon studies conducted in China were combined and analysed (Lubin *et al.*, 2004). The studies included 1050 lung cancer cases and 1996 controls. In the pooled data, odds ratios increased significantly with greater radon concentration. Based on a linear model, the odds ratio was 1.33 (95%CI: 1.01–1.36) at radon exposure levels of 100 Bq/m^3. For subjects who lived in a home for 30 years or more, the odds ratio at 100 Bq/m^3 was 1.32 (95%CI: 1.07–1.91).

(d) Ecological studies of residential radon and lung cancer

Cohen & Colditz (1995) reported a negative correlation between radon levels and lung cancer in over 3000 counties in the USA. Such ecological studies are subject to several limitations, including the absence of county-specific data on smoking, which can confound the association between ecological indicators of radon exposure and lung cancer risk. This possibility was confirmed by (Puskin, 2003), who subsequently reported that negative correlations were obtained between county-level radon concentrations and county-level cancer occurrence rates for cancers known to be related to tobacco smoking, with no correlation at the ecological level between radon and cancers not related to tobacco smoking. Similarly, Lagarde & Pershagen, (1999) demonstrated that an increasing trend in lung cancer risk with increasing exposure to indoor radon observed in a national Swedish case–control study became a decreasing trend when information on radon and lung cancer was aggregated to the ecological (county) level.

(e) Attributable risk of lung cancer

Darby *et al.* (2005) estimated the fraction of the lung cancer burden attributable to indoor radon in Europe to be about 9%, based on the relative risk of lung cancer associated with exposure to indoor radon in the combined analysis of the 13 European case–control studies, and the indoor radon concentrations observed in those studies. In the USA, the BEIR VI committee (BEIR VI, 1999) used the radon risk projection models developed on the basis of the miner data, and data on radon concentrations in US homes to estimate the attributable fraction to be in the range of 10–15%, depending on which of the committee's two preferred risk models was used. Brand *et al.* (2005) used the BEIR VI risk models and data on radon concentrations in Canadian homes to obtain an estimate of the attributable fraction of 8%. Although subject to some uncertainty, these results suggest that about 8–15% of the lung cancer deaths in Europe and North America may be attributed to residential radon exposure, making radon the second leading cause of lung cancer death after tobacco smoking in those regions.

(f) Studies of leukaemia

Lubin *et al.* (1998) conducted a case–control study of acute lymphoblastic leukaemia among children under 15 years of age in the USA in relation to residential radon exposure (see Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.7.pdf), based on 1-year track-etch radon measurements in all current and previous residences in which they had lived for at least 6 months. This study provided no evidence of an association between indoor radon exposure and childhood acute lymphoblastic leukaemia. In a subsequent case–control study of leukaemia and central nervous system (CNS) tumours (nephroblastoma, neuroblastoma, and rhabdomyosarcoma), Kaletsch *et al.* (1999) found no evidence of an increased risk of leukaemia of children under 15 years of age in Lower Saxony, Germany. Steinbuch *et al.* (1999) reported no increase in the risk of acute myeloid leukaemia of children under 18 years of age identified through the Children's Cancer Group, which involves over 120 institutions in the USA and Canada. Law *et al.* (2000a) did not find evidence of an increased risk of either acute lymphoblastic leukaemia or acute myeloid leukaemia in adults 16–69 years of age in the United Kingdom. Results from the United Kingdom Childhood Cancer Study, which included 805 cases of acute lymphoblastic leukaemia, demonstrated no association between residential radon and leukaemia (Cartwright *et al.*, 2002). Raaschou-Nielsen (2008) conducted a case–control study of 2400 cases of leukaemia, CNS tumours, and malignant lymphoma in children under 15 years of age identified through

the Danish Cancer Registry. Cumulative radon exposure was associated with an increased risk of acute lymphoblastic leukaemia, with an odds ratio of 1.63 (95%CI: 1.05–1.23) for children exposed to more than 890 Bq/m^3–years, relative to children exposed to less than 160 Bq/m^3–years. [The Working Group noted that a strength of this study was the inclusion of virtually all relevant cases in Denmark.]

Several ecological studies and surveys suggested a positive correlation between exposure to indoor radon and the risk of adult acute leukaemia (especially myeloid leukaemia) and childhood leukaemia (Henshaw *et al.*, 1990; Haque & Kirk, 1992; Kohli *et al.*, 2000; Evrard *et al.*, 2006). These studies were based on an ecological design in which radon levels were regressed against the incidence of several cancer sites. Average radon concentrations were obtained from national or county surveys, and recorded as population-averaged arithmetic means. In some cases, crude geographic or geological features of the inhabited areas were used to derive estimates of levels of radiation emission, and subsequently used as surrogates for exposure assessment (Forastiere *et al.*, 1992). [The Working Group noted that this type of study design has many limitations, including a lack of measurement of individual exposure to indoor radiation, a lack of control population, the difficulty in separating radon effect from that of indoor γ-radiation, and the absence of multiple regression analyses of potential confounders (Eatough & Henshaw, 1994). In addition, ecological studies were often based on the assumption that national or regional radon concentrations apply to areas where cancer registries have been compiled.]

(g) Cancers other than lung and leukaemia

In addition to leukaemia, the case–control study conducted by (Kaletsch *et al.*, 1999) in Germany examined the association between indoor radon and solid tumours. An elevated odds ratio of 2.61 was reported (95%CI: 0.96–7.13) for radon exposures above 70 Bq/m^3 relative to lower exposures; and this finding was based mainly on six CNS tumours, for which the odds ratio was 3.85 (95%CI: 1.26–11.81). The United Kingdom Childhood Cancer Study examined the association between indoor radon and non-Hodgkin lymphoma, Hodgkin disease, CNS tumours, and other solid tumours, and found no association with any of these tumours (Cartwright *et al.*, 2002). The case–control study by Raaschou-Nielsen (2008) in Denmark found no association between indoor radon and either tumours of the central nervous system or malignant lymphoma.

Ecological studies have suggested that several cancers might also be weakly correlated with indoor radon, especially kidney cancer, prostate cancer, malignant melanoma, and some childhood cancers (Butland *et al.*, 1990; Axelson, 1995). However, these studies use ecological indicators of radon exposure, and do not control for possible confounders such as indoor γ-radiation or tobacco smoking.

2.1.3 Synthesis

Cohort studies of underground miners exposed to high levels of radon (specifically, ^{222}Rn and its decay products) in the past have consistently demonstrated an increased risk of lung cancer, providing *sufficient evidence* of carcinogenicity in humans (IARC, 1988). Case–control studies of residential radon and lung cancer have added to the weight of epidemiological evidence linking radon to lung cancer (IARC, 2001).

Since then, combined analyses of data from seven case–control studies of indoor radon and lung cancer in North America (Krewski *et al.*, 2005, 2006), 13 case–control studies in Europe (Darby *et al.*, 2005, 2006), and two studies in China (Lubin *et al.*, 2004) have provided clear evidence of an increased risk of lung cancer due to radon (specifically, ^{222}Rn and its decay products) in homes. A large study of uranium miners in

Germany (Grosche *et al.*, 2006) and a joint study in France and the Czech Republic (Tomášek *et al.*, 2008) have reaffirmed previous findings of increased risk of lung cancer in underground miners exposed to radon.

Cohort studies of underground miners permit an assessment of cancer risk at multiple sites; and some evidence of an increased risk of leukaemia was reported among Czech uranium miners, although these miners were also exposed to γ-radiation (a risk factor for leukaemia). Case–control studies of childhood and adult leukaemia in relation to indoor radon exposure have mostly not shown elevated risks, although one study suggested an increased risk of leukaemia among children in Denmark. An increased risk of solid tumours was seen in one case–control study in Germany; however, this result was based on only six CNS tumours, and was not confirmed in other case–control studies.

IARC (1972, 1987, 1988) previously concluded that haematite miners exposed to radon were at increased risk of lung cancer. A subsequent study of haematite miners in China demonstrated increasing lung cancer risk with increasing radon concentrations; however, a similar trend was seen with increasing dust concentrations, and it was not possible to separate the effects of radon and dust in this study. The Working Group reaffirmed the conclusion reached in the earlier IARC evaluations that radon contributes to the increased lung cancer risk seen in haematite miners.

2.2 α-Particle emitters

2.2.1 Radium-224/226/228

The previous *IARC Monograph* evaluation of radium-224, radium-226, and radium-228 IARC (2001) was based on an increased risk of bone sarcoma associated with all three isotopes, as well as an increased risk of paranasal sinuses and mastoid process associated with ^{226}Ra, in cohorts of radium watch-dial painters who ingested ^{226}Ra (often in combination with ^{228}Ra), and patients injected with ^{224}Ra. Few epidemiological analyses of cancer risk following radium exposure have been published since then. One of these is an update to a cohort study of patients injected with ^{224}Ra in Germany (Wick *et al.*, 2008), while two recent case–control studies in the USA and Thailand have considered radium in drinking-water (Guse *et al.*, 2002; Hirunwatthanakul *et al.*, 2006).

(a) Bone

The cohort studies of cancer risk among radium watch-dial painters in the USA were initially carried out at the Massachusetts Institute of Technology (Rowland *et al.*, 1978) and the Argonne National Laboratory (Stebbings *et al.*, 1984; Carnes *et al.*, 1997), and later combined (Rowland *et al.*, 1983; Spiers *et al.*, 1983). Those studies, in which some of the painters ingested ^{226}Ra (often in combination with ^{228}Ra) by the practice of 'pointing' their paintbrush tips with their lips, showed consistent increases in the risk for bone sarcoma related to exposure to α-particles (Rowland *et al.*, 1978; Stebbings *et al.*, 1984; see Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.8.pdf). Carnes *et al.* (1997) reported that both isotopes of radium contributed significantly and independently to the rate of mortality from bone sarcomas in multivariate analyses of dose–response relationships in which the two isotopes were included as separate variables. The excess risk for carcinomas of the paranasal sinuses and mastoid process was associated with internally deposited ^{226}Ra, but probably not ^{228}Ra (Rowland *et al.*, 1978). On the other hand, in the studies of British dial painters who were exposed to lower doses (none of them engaged in brush pointing), no bone sarcomas were observed (Baverstock & Papworth, 1985).

No further updates of bone cancer among radium watch-dial painters have been published

in recent years, but new analyses using data from the US studies have appeared. Bijwaard *et al.* (2004) developed two-mutation mechanistic models fitting animal and human data on bone cancer. They reported that the results using data for watch-dial painters agree well with those for studies of radium-exposed beagles. The best fit for the watch-dial painters had equal cell killing terms in both mutation rates, but a nearly equally well-fitting model could be constructed with cell killing only in the second mutation rate, as in the analysis of beagle data. In an analysis of data on bone and sinus cancers for radium watch-dial painters using a two-mutation model, Leenhouts & Brugmans (2000) reported that the model parameters from the best fit were consistent with cellular radiobiological data. The fitted dose–response relationships were linear–quadratic with radium intake and with α-particle radiation dose, and did not support a model involving a threshold dose. The risks at low doses were estimated to be about a factor of 10 lower than those based on a linear extrapolation from high doses.

Bone sarcomas were the major late effect among patients with tuberculosis, ankylosing spondylitis, and other diseases who were treated with high doses of ^{224}Ra (mean bone surface dose, 30 Gy) in a cohort study in Germany (Nekolla *et al.* 2000; see Table 2.8 on-line). Nekolla *et al.* (2000) used an improved dosimetry system – relative to previous analyses in that cohort – with modified doses to the bone surface, particularly for exposures at younger ages. Virtually all of the tumours in the cohort could be attributed to exposure to radium, reflecting the very high bone-surface doses received. In contrast to previous analyses of this cohort, the excess absolute risk (EAR) decreased with increasing age at exposure. As before, the EAR for a given total dose decreased with increasing duration of exposure; however, there was little evidence of such an effect at the lower doses received by this cohort, which was suggested to be in agreement with microdosimetric considerations and general radiobiological experience (Nekolla *et al.*, 2000). Among ankylosing spondylitis patients treated with lower doses of ^{224}Ra (mean bone-surface dose, 5 Gy) in another German cohort, there was an excess of bone cancer relative to population rates, but based on only four cases (Wick *et al.*, 1999).

A case–control study of osteosarcoma in Wisconsin (USA) looked for any correlation with estimated levels of total α-particle activity and levels of ^{226}Ra and ^{228}Ra in drinking-water, by linking measurements to Zone Improvement Plan (ZIP) codes (Guse *et al.*, 2002; see Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.9.pdf). No evidence of an association was found. However, the study lacked individual exposure data, other than ZIP code. In addition, the exposures were much lower than those for the ^{226}Ra watch-dial painters.

(b) *Leukaemia*

Wick *et al.* (2008) and Nekolla *et al.* (1999, 2000) reported findings for leukaemia in two separate cohorts of ankylosing spondylitis patients in Germany (see Table 2.8 on-line). Exposures from ^{224}Ra in the former cohort were lower than those in the latter cohort. Wick *et al.* (2008) found a significantly raised risk of leukaemia – particularly myeloid leukaemia – relative to population rates, which was in line with experimental findings from mice injected with varying amounts of this radionuclide. Nekolla *et al.* (1999) reported eight leukaemia cases in their cohort, compared with 3.8 expected from population rates (P = 0.04). When a 2-year lag was used, the corresponding P value was 0.08. [The Working Group noted that although there were indications of raised leukaemia risks in both of the ^{224}Ra cohorts, these findings were based on small numbers of cases and that dose–response analyses were not performed.]

No excess incidence of leukaemia was observed among watch-dial painters or among watch-dial

painters with measured body burdens in the USA (Spiers *et al.*, 1983). However, leukaemia occurred early in female watch-dial painters and an excess of leukaemia was observed among male watch-dial painters (Stebbings, 1998).

(c) Other cancers

Little information has appeared since the previous *IARC Monograph* (IARC, 2001) on the association between exposure to radium and risk of cancers other than bone cancer and leukaemia. In particular, there are no new findings for the radium watch-dial painters nor from the ^{224}Ra medically exposed cohorts. The excess risk for carcinomas of the paranasal sinuses and mastoid process seen among US radium watch-dial painters was associated with internally deposited ^{226}Ra, but probably not ^{228}Ra (Rowland *et al.*, 1978). In particular, these cancers occurred mainly among subjects exposed to ^{226}Ra only, and infrequently among those exposed to both ^{226}Ra and ^{228}Ra (Rowland *et al.*, 1978). High ^{222}Ra levels were found in the mastoid cavity of subjects whose body burdens were primarily from ^{226}Ra, and suggested that radioactive decay of ^{222}Ra released into this cavity by decay of ^{226}Ra in the surrounding bone is the cause of these cancers (Evans, 1966).

In a cohort of USA radium watch-dial painters, suggestive positive associations were observed between estimated radium body burden and lung cancer and multiple myeloma. These cancers, particularly multiple myeloma, were more closely associated with duration of employment than with radium intake (Stebbings *et al.*, 1984). [The Working Group noted that duration of employment corresponded to duration of γ-radiation exposure, and was a surrogate for cumulative external γ-radiation dose.] No increased risk of lung cancer was observed in cohorts of patients injected with ^{224}Ra (Nekolla *et al.*, 1999; Wick *et al.*, 1999).

Stebbings *et al.* (1984) also reported an association between estimated radium burden and mortality from breast cancer in US radium watch-dial painters. This association may have been confounded; in particular, women who had worked the longest and had had both heavier exposure to γ-radiation from radium and higher breast cancer rates tended to have chosen not to have children. A raised risk of breast cancer was also observed in a cohort of women in the United Kingdom who worked with radium paint (one sided $P = 0.077$) (Baverstock *et al.*, 1981). Due to small body burden of radium compared to the US luminizers, no further analyses were performed with regard to α-particles. In analyses stratified for both age at start of luminizing (< 30 versus ≥ 30 years) and γ-radiation dose (< 0.2 versus ≥ 0.2 Gy), the excess risk was seen to be predominant among the younger age group receiving ≥ 0.2 Gy of γ-radiation (one-sided $P = 0.009$). Nekolla *et al.* (1999) reported a significantly raised risk of breast cancer among patients injected with ^{224}Ra. Such an association was not observed among patients injected with low-dose ^{224}Ra (Wick *et al.*, 1999). [The Working Group noted indications of a raised breast cancer risk in an unexposed group in the analysis conducted by Nekolla *et al.* (1999), suggesting that factors other than radiation may have contributed to the breast cancer excess seen in the exposed group].

Statistically significant increases in risk of soft-tissue sarcomas, kidney cancer, urinary bladder cancer, liver cancer and thyroid carcinoma were also reported among patients injected with high doses of ^{224}Ra (Nekolla *et al.*, 1999), but not among those who received low doses (Wick *et al.*, 1999). [The Working Group noted that although significant increases for the aforementioned types of cancer were reported by Nekolla *et al.* (1999) relative to population rates (Table 2.8 on-line), the corresponding data for a control group of unexposed patients were not presented. For the other ^{224}Ra cohort, Wick *et al.* (1999) presented results for both exposed and unexposed patients (Table 2.8 on-line). However,

in both cohorts, the numbers of cases of specific cancer types were generally small.]

In Thailand, a case–control study of cancers of the upper digestive tract reported a statistically significant association with intakes of radium in drinking-water, based on small numbers of cases (Hirunwatthanakul *et al.*, 2006; Table 2.9 on-line). [The Working Group noted that in contrast to the other study on radium in drinking-water (Guse *et al.*, 2002), this study collected information on individuals' daily consumption of drinking-water and on other potential risk factors, although for the cancer cases (but not the controls) this information was provided mainly by relatives.]

(d) Synthesis

As discussed previously by IARC (2001), the studies of cancer risk among US radium watch-dial painters showed consistent increases in the risk for bone sarcoma related to exposure to α-particles, and both ^{226}Ra and ^{228}Ra contributed significantly and independently to this elevated risk. The previous Working Group (IARC, 2001) associated the excess risk for carcinomas of the paranasal sinuses and mastoid process in this cohort to internally deposited ^{226}Ra, but probably not ^{228}Ra. No further data was available to the Working Group that altered the conclusions in the previous *IARC Monograph*.

The most recent analysis of the risk of bone tumours among patients treated with ^{224}Ra for tuberculosis or ankylosing spondylitis supports the strong association observed by the previous Working Group (IARC, 2001).

There is some evidence of elevated leukaemia risks in the two cohorts of patients injected with ^{224}Ra cohorts. However, these findings were based on small numbers of cases, and dose–response analyses were not performed. No excess incidence of leukaemia was observed among US radium watch-dial painters overall. The possibility that radium isotopes increase leukaemia risk in humans cannot be ruled out, but the available evidence did not permit any causal relationship to be established.

2.2.2 Mixed α-particle emitters

(a) Thorium-232

The previous IARC evaluation of ^{232}Th and its decay products, administered intravenously as a colloidal dispersion of ^{232}Th dioxide, was based on increased risk of primary liver cancer, including haemangiosarcomas, and leukaemia, excluding chronic lymphocytic leukaemia (IARC, 2001).

The evidence of cancer risk associated with Thorotrast (stabilized ^{232}Th dioxide) exposures came mainly from cohort studies in Denmark, Germany, Japan, Portugal, and Sweden (IARC, 2001). Thorotrast was used extensively in medical practice between the 1930s and the 1950s as a radiographic contrast agent. Owing to its colloidal nature, Thorotrast is retained mostly in the reticuloendothelial system (liver, spleen, and bone marrow) after intravenous injection.

(b) Liver and biliary tract cancers

Cohort studies in Denmark, Germany, Japan, Portugal, Sweden, and the USA demonstrated significantly increased risks for liver cancer (approximately one-third being haemangiosarcomas), which were significantly correlated with the volume of Thorotrast injected. The incidence of and mortality from liver cirrhosis were also significantly increased in all studies in which liver cirrhosis was an end-point (Mori *et al.*, 1999; dos Santos Silva *et al.*, 2003). A combined analysis of the cohorts of Danish and Swedish Thorotrast patients (Travis *et al.*, 2003) showed statistically significant trends with a surrogate measure for cumulative radiation dose in the incidence of primary liver cancer and cancer of the gallbladder. [The Working Group noted that key strengths of this analysis were the long-term follow-up, the availability of cancer incidence data, the large number of cases observed and the opportunity to conduct a dose–response

analysis, albeit based on a surrogate measure.] Among patients injected with 20 mL or more of Thorotrast, the cumulative excess cancer incidence remained elevated for up to 50 years, and approached 97%. Analysis of a smaller cohort of Thorotrast patients in the USA, based on mortality data, yielded comparable findings (Travis *et al.*, 2003). An extended mortality follow-up of Thorotrast patients in Portugal (dos Santos Silva *et al.*, 2003) showed statistically significant trends with a surrogate measure for cumulative radiation dose for all cancers combined, and for the grouping of liver cancer and chronic liver diseases. Becker *et al.* (2008) described an extended follow-up of mortality in the German Thorotrast cohort, which is the largest single study of Thorotrast patients. By the end of 2004, nearly all of these patients had died. For all malignant neoplasms and for cancers of the liver and intrahepatic bile ducts, both the SMR and the relative risk compared to a control group increased with increasing time since first exposure. An earlier analysis of the German cohort (van Kaick *et al.*, 1999) reported associations between the amount of Thorotrast injected and mortality from cancers of the liver, gallbladder and extrahepatic bile ducts. A Japanese cohort (Mori *et al.*, 1999) also showed increased mortality from liver cancer among Thorotrast patients. In this publication, the risk associated with increasing time since first exposure was also reported, but no formal statistical test for trend was presented (see Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.10.pdf).

Results of the continued follow-ups of Thorotrast exposed patients are summarized in Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.11.pdf.

(c) Haematological malignancies

A significantly increased risk of leukaemia excluding chronic lymphocytic leukaemia has been reported in the Thorotrast cohorts in Denmark, Germany, Japan, Portugal, Sweden, and the USA. A combined analysis of the cohorts of Danish and Swedish Thorotrast patients (Travis *et al.*, 2003) in which the incidence of leukaemias (excluding chronic lymphocytic leukaemia) was significantly higher than that among unexposed patients showed no statistically significant trend in incidence associated with this dose measure. Analysis of a smaller cohort of Thorotrast patients in the USA, based on mortality data, yielded comparable findings (Travis *et al.*, 2001). In an extended mortality follow-up of Thorotrast patients in Portugal (dos Santos Silva *et al.*, 2003), mortality from benign and malignant haematological diseases and from leukaemia (excluding chronic lymphocytic leukaemia) remained high relative to national rates over the follow-up period (more than 40 years after administration of Thorotrast), but did not show a trend with the surrogate dose measure. In an extended follow-up of mortality in the German Thorotrast cohort (Becker *et al.* (2008), statistically significantly elevated risks were seen for malignancies of the haematopoietic system (particularly myeloid leukaemia). An earlier analysis of the German cohort (van Kaick *et al.*, 1999) reported associations between the amount of Thorotrast injected and mortality from a grouping of myeloid leukaemia and myelodysplastic syndrome (see Table 2.10 on-line).

(d) Other cancers

Increased risks for cancers at other sites were reported in some studies but not consistently. A combined analysis of the cohorts of Danish and Swedish Thorotrast patients (Travis *et al.*, 2003) showed statistically significant trends with a surrogate measure for cumulative radiation dose in the incidence of cancers of the pancreas,

peritoneum and other digestive organs. [The Working Group noted that the excess risks for site-specific cancers should be interpreted with caution because of the potential bias associated with the selection of cohort participants, non-comparability of the internal and external comparison groups, and confounding by indication.] In an extended follow-up of mortality in the German Thorotrast cohort (Becker *et al.*, 2008), statistically significantly elevated risks were seen for cancer of the pancreas, brain, and prostate. The earlier analysis of the German cohort by van Kaick *et al.* (1999) did not find a raised risk for cancer of the prostate, but this analysis (unlike the most recent analysis by Becker *et al.*, 2008) did not take into account the different age distributions of the exposed and unexposed groups (See Table 2.10 on-line).

The Thorotrast studies give mixed results on lung cancer risk (See Table 2.11 on-line), although patients given Thorotrast exhale high concentrations of ^{220}Rn (thoron). [The Working Group noted that the interpretation of these findings is hampered by the lack of information on smoking.] Studies in the USA and China of workers exposed to thorium by inhalation of fine particles containing thorium and its decay products reported a raised risk of lung cancer relative to national rates and – in an updated analysis of miners in China (Chen *et al.*, 2003) – relative to an unexposed control group (see Table 2.10 on-line). However, this latter study did not incorporate a dose–response analysis. Furthermore, the presence in the Chinese mines of silica dioxide and rare-earth elements raises concerns about possible confounding. The other occupational study – of thorium workers in the USA – did not show an association between lung cancer and potential for thorium exposure (Liu *et al.*, 1992; Table 2.10 on-line). Furthermore, data on smoking were not available for either of these occupational studies.

(e) Synthesis

Results of the continued follow-up studies of patients exposed to Thorotrast continue to show raised risks several decades after first exposure for all malignant neoplasms combined, with consistently large relative risks seen for liver cancer and malignancies of the haematopoietic system. The risk of liver cancer increased with increasing values for a surrogate of radiation dose in analyses of the Danish/Swedish, German, Portuguese, and US cohorts.

An earlier analysis of the German cohort reported an association between a measure of radiation dose and mortality from myeloid leukaemia and myelodysplastic syndrome. In contrast, analyses of the grouping of haematopoietic malignancies in the Danish/Swedish, Portuguese and US cohorts did not show an association with a surrogate of dose; however, these analyses were not conducted specifically for leukaemia other than chronic lymphocytic leukaemia in the Portuguese and US cohorts.

Large increased risks of cancers of the extrahepatic bile ducts and of the gallbladder were reported in the two largest analyses of Thorotrast patients (Table 2.11 on-line). In view of their integral relationship to the liver, in which most of the injected Thorotrast is deposited, the extrahepatic bile ducts are likely to receive substantial α-particle exposure. Although the gallbladder is a minor site of Thorotrast storage, its location on the visceral surface of the liver may lead to continual α-particle exposure.

Pancreatic cancer risk is elevated in the German and Danish/Swedish Thorotrast cohorts, although the relative risks tend to be lower than those for the aforementioned cancer sites (Table 2.11 on-line). In the latter cohort, there is also borderline evidence of an association with a surrogate measure of radiation dose. Doses to the pancreas are likely to be notably lower than these to the liver or spleen, although the anatomical juxtaposition of a portion of the pancreas to the

spleen may have led to higher doses. However, information on smoking habits is lacking in these studies. Prostate cancer is also significantly elevated in the German and Danish/Swedish Thorotrast cohorts (Table 2.11 on-line), although there has been no analysis of prostate cancer risk in relation to the amount of Thorotrast injected or any other measure of radiation exposure. Doses to the prostate are likely to be small relative to those for organs such as the liver.

Raised risks have also been reported among Thorotrast patients for several other types of cancer, although the interpretation of these findings is unclear largely because of possible confounding by factors that led to the exposure. This is particularly important for brain cancer because many of these patients were examined with Thorotrast for cerebral angiography.

Studies of workers exposed to thorium by inhalation of fine particles containing thorium and its decay products, together with some – but not all –studies of Thorotrast patients have reported raised risks of lung cancer. However, possible differences in smoking habits, and – among miners – possible confounding by other exposures must also be considered.

Overall, large, statistically significant relative risks between exposure to Thorotrast and primary liver cancer, leukaemia (excluding chronic lymphocytic leukaemia), cancers of the extrahepatic bile ducts, and cancer of the gallbladder have been observed in the two largest analyses and, in several instances, show associations with measures of exposure. For pancreatic and prostate cancers, significantly raised risks were observed in the two largest analyses but these risks are lower than those for aforementioned cancer types and confounding cannot be excluded. No substantive new evidence on cancer risks following inhalation of ^{232}Th has appeared since the publication of the previous *IARC Monograph* (IARC, 2001).

2.2.3 Plutonium

The previous IARC evaluation of plutonium was based on an increased risk of lung cancer, liver cancer and bone sarcoma. That Working Group noted that human exposure to ^{239}Pu could also include exposure to ^{240}Pu (IARC, 2001).

Plutonium is an element used mostly for nuclear weapons production, and the production of mixed oxide fuels. Most of the exposure to plutonium is among workers involved in chemical or mechanical processing of plutonium and in nuclear weapons or nuclear power production. Several large groups of workers exposed to plutonium have been studied in the USA, United Kingdom, and the Russian Federation. Exposures have occurred since the 1940s when weapons-grade plutonium production was started in those countries. Several accidents also exposed people not working in the above industries to plutonium.

The major exposure pathways to plutonium are inhalation and, to a much lesser extent, wounds (the latter takes place mostly in workers). Only a small percentage of plutonium entering the gut is absorbed into blood, and consequently ingestion is not usually a major exposure pathway. After inhalation intake, plutonium is redistributed in the body, and is retained mostly in lung, liver and bone, which receive the largest doses from incorporated plutonium.

The previous IARC evaluation was primarily based on a cohort of workers employed at the Mayak plant in the Russian Federation, where exposure to plutonium (mostly ^{239}Pu) was substantial. Dose–response relationships were demonstrated for cancers of the lung, liver and bone in both men and women exposed to a broad range of doses. Cancers at other sites were not studied at the time. The results of the most informative studies from the previous *IARC Monograph* and of newer studies are summarized in Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.12.pdf

and Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.13.pdf.

(a) Cancer of the lung

In a recent analysis of data from Hanford plant, USA, potential for exposure to plutonium was classified in three groups (minimal, non-routine or limited, and routine potential) using a job-exposure matrix (Wing *et al.*, 2004). Mortality rates for non-external causes of death, all cancers, plutonium-related cancers (lung, liver, bone and connective tissue, and lymphatic tissue cancers), and some other cancers were lower in workers with potential routine or non-routine exposure to plutonium than in other Hanford workers [probably due to healthy worker effect]. However, mortality from all cancers, plutonium-related cancers, and lung cancer was associated with duration of employment in jobs with routine potential for plutonium exposure.

Lung cancer mortality among workers at the Rocky Flats plant was analysed in a nested case–control study by Brown *et al.* (2004) and Brown & Ruttenber (2005); Table 2.13 on-line). Lung doses from incorporated plutonium were assessed by a model based on Publication 30 of the International Commission on Radiological Protection (ICRP, 1979). External dosimetry data were extracted from computerized records of individual workers. Exposure levels ranged up to hundreds mSv of plutonium lung dose and tens of mSv of external dose. Using dose estimates to the lung epithelium, a statistically significant risk of lung cancer was found when plutonium exposure was characterized in terms of the dose of α-particles to the lung epithelium. [The Working Group noted that this study did not include adjustment for smoking as the authors reported that the odds ratios were not changed by more than 10%. Later, Brown & Ruttenber (2005) stated that smoking was not confounding the relationship between the dose of α-particles to the lung and the risk from lung cancer mortality.]

Several analyses of lung cancer mortality among Mayak workers have been published; a series of earlier publications were reviewed in the previous *IARC Monograph* (IARC, 2001). The analyses by Kreisheimer *et al.* (2000) were restricted to reactor workers (assumed to have zero plutonium lung dose), and radiochemical or plutonium workers with estimates of plutonium body burden and lung dose. Analyses were conducted within the cohort, rather than through comparisons with Russian population rates. Lung cancer mortality was associated with lung dose from plutonium, but not external dose. [The Working Group noted that no adjustment was made for smoking in this analysis]. In an extended follow-up, using new dosimetry data and smoking information, Kreisheimer *et al.* (2003) analysed lung cancer mortality among men in the same cohort. External dose was not associated with lung cancer mortality in this study whereas a highly significant dose–response association was seen for plutonium lung dose. There was no departure from linearity for the effect of plutonium.

The above study (Kreisheimer *et al.*, 2003) was restricted to workers monitored for plutonium and only from the time they were monitored. To allow for better analyses of external dose–response relationship for the workers who were not monitored, a surrogate characteristic of potential exposure to plutonium was developed based on detailed occupational history data of Mayak workers (Khokhryakov *et al.*, 2000; Krahenbuhl *et al.*, 2005), and was used in analyses published by Shilnikova *et al.* (2003), Gilbert *et al.* (2004), and Sokolnikov *et al.* (2008). A significant dose-related increase in lung cancer risk was demonstrated by Gilbert *et al.* (2004). The ERR of lung cancer at age 60 in women was 4 times higher than in men, reflecting very different background lung cancer rates in men and women. No departure from linearity was found for plutonium lung dose and lung cancer. For the subcohort of workers hired during 1948–58, analyses

were repeated restricting the cohort to those monitored for plutonium, reactor and auxiliary workers, and to those who also had available smoking status (as a yes/no variable) information (Gilbert *et al.*, 2004). Following adjustment for smoking, the ERR/Gy for internal dose was changed only slightly in both men and women and the women/men ratio of the ERR/Gy was not greatly modified. The analysis of Sokolnikov *et al.* (2008) was restricted to workers with at least 5 years of follow-up. Smoking data were available for the full cohort. A surrogate measure of potential to plutonium exposure was used for workers not monitored for plutonium (or until they were monitored). A significantly increased smoking-adjusted risk of lung cancer was found in workers with total accumulated plutonium lung dose in the range of 0.2–0.3 Gy and above. There was no departure from linearity. Smoking habits in the cohort of Mayak workers showed striking differences between genders, with 75% of men and only 4.2% of women reporting smoking.

The association between lung cancer risk and exposure to plutonium among Mayak workers was also demonstrated in other analyses (Jacob *et al.*, 2005; Jacob *et al.*, 2007).

(b) Cancer of the liver and bone

Initially, in a cohort of early Mayak workers who received largest doses of both external and plutonium exposures, the analyses of bone and liver cancer mortality were done using plutonium body-burden levels (Gilbert *et al.*, 2000; Koshurnikova *et al.*, 2000). All analyses were stratified by age, calendar year, and gender, and adjusted for external dose. Among bone and soft-tissue cancers, included were only those that developed in sites directly adjacent to the bone where plutonium exposure could take place. Bone cancer mortality was significantly increased in workers with extremely high plutonium body–burden levels. The same was true for liver cancer mortality, although liver cancer risks in men and women differed substantially (Gilbert *et al.*, 2000) [The Working Group noted that this was probably due in part to gender differences in background mortality (mostly related to different alcohol habits)]. Of 60 liver cancers identified in this subcohort, 10 were haemangiosarcomas, which are liver tumours found among subjects exposed to extremely high levels of α-particles (such as exposed to Thorotrast) [The Working Group noted that plutonium workers are currently not known to be exposed to vinyl chloride, a chemical which is strongly associated with liver haemangiosarcoma (IARC, 2008)]. One of limitations of the Mayak workers' cohort is the incomplete coverage of plutonium monitoring. However, among plutonium workers that were not monitored for internal exposure, the risk of death from bone and liver cancer was significantly higher compared to reference population.

A follow-up analysis using improved dosimetry conducted in 2008 focusing on absorbed dose to the bone and liver, rather than body burden, confirmed the original results (Sokolnikov *et al.*, 2008). Although bone and liver cancer among Mayak workers are indicative for plutonium effects, the small number of cases results in some uncertainty about the shape of the dose–response relationship for these tumour sites.

(c) Other cancers

McGeoghegan *et al.* (2003) analysed mortality and cancer morbidity of female workers employed at British Nuclear Fuels Limited (BNFL) and the Atomic Energy Agency, in the United Kingdom. The overall and the majority of site-specific SMRs for radiation workers other than plutonium workers were lower when compared to the population of England and Wales; SMRs for all causes and all malignant cancers were significantly lower. On the other hand, compared to other radiation workers, mortality from all causes, all malignant cancers and breast cancer in plutonium workers were significantly higher. The ratio of SMR in plutonium workers to other radiation workers was 2.20 for all causes ($P < 0.01$), 3.30

for all malignant cancers ($P < 0.01$), and 3.77 for breast cancer ($P < 0.05$).

Analyses of Mayak workers published by Shilnikova *et al.* (2003) demonstrated a statistically significant increased risk of solid cancers other than lung, liver and bone in relation to systemic body burden (i.e. whole body excluding lung). [The Working Group noted that it was unlikely that exposure to other carcinogens could account for these findings.] However, the absence of organ-specific doses precluded analyses on specific solid cancers. There was no significant risk of leukaemia related to exposure to plutonium; the point estimate for the plutonium body burden dose–response with regard to leukaemia death was negative but not statistically significant ($P > 0.5$).

(d) Synthesis

Analyses of cancer risk following exposure to plutonium in Mayak workers show evidence of plutonium carcinogenicity primarily in lung, liver and bone, the organs in which high doses of incorporated plutonium are accumulated. Risks were seen to increase in a dose-dependent manner. Recent analyses demonstrated that increased lung cancer risks remained after adjustment for tobacco smoking.

Analyses of Mayak workers also demonstrated an increased risk of solid tumours other than lung, liver and bone in relation to exposure to plutonium. However, site-specific analyses were not conducted. Little information was available on the association between exposure to plutonium and leukaemia.

2.2.4 Uranium

All isotopes of uranium are radioactive. Naturally occurring uranium consists of a mixture of three radiactive isotopes: ^{234}U (0.005%), ^{235}U (0.711%), and ^{238}U (99.284%) (IAEA, 2004). ^{234}U is a pure α-particle emitter, and ^{235}U and ^{238}U are mixed α-particle emitters with other emissions of β-particles and γ-radiation. Therefore, external exposure to natural or depleted uranium, and internal deposition of uranium, implies exposure to α- and β-particles and γ-radiation (Bleise *et al.*, 2003). In some settings, bremsstrahlung radiation (photons) is also present due to the interaction of β-particles from uranium decay with dense material. Uranium may also have chemical toxicity effects. Due to the very long half-life of its main isotope (^{238}U; 4.5 x 10^9 years), natural uranium is considered a low specific radioactive element. Epidemiological research on the health effects of exposure to natural and depleted uranium is made difficult by the typically low dose rates associated with such exposures.

Occupational exposure to natural uranium happens in the civil nuclear industry and the atomic weapons industry especially from the mining and processing of uranium ores (insoluble oxides) or as exposure to "yellowcake," the soluble form of the oxide (UO_4), in the chemical purification of uranium. Natural uranium may also be a component of drinking-water (Kurttio *et al.*, 2002). Uranium millers and individuals involved in other uranium-processing operation may be exposed to α- and β-particles from inhaled or ingested uranium dust. Inhalation of insoluble uranium particles is the major pathway of exposure for the lung (IARC, 2001). Inhaled or ingested soluble uranium that becomes systemic may have more chemotoxicity than radiotoxicity. The use of depleted uranium munitions, including enforced armour-piercing projectiles and tank armour, may increase the exposure of certain populations to uranium. The oxide dust produced by the impact of the elemental munition on hard targets has a soluble component. The impact also releases insoluble uranium metal from fragments (Bleise *et al.*, 2003).

Of four studies that were considered in the previous *IARC Monograph* (Polednak & Frome, 1981; Dupree *et al.*, 1987; Checkoway *et al.*, 1988; Ritz, 1999), all of which were occupational cohorts, updated results were later published

for two larger studies. This section reviews the epidemiological literature published since the previous *IARC Monograph*. Given the radiological properties of uranium, it should be noted that the independent carcinogenic effects of exposure to γ-radiation, β-particle radiation, and α-particle radiation are covered in separate sections of this volume. This review of the epidemiological literature focuses on studies of worker populations in which large numbers of people were exposed to relatively high levels of uranium as a consequence of milling, enrichment, or fabrication processes, and studies of populations that were exposed to depleted uranium. Studies of uranium miners are excluded from this review because their exposure is primarily to radon (and radon daughters) which are covered in a separate section of this *Monograph*, and not repeated here. Similarly, workers in the nuclear power industry and weapons industry who worked in settings where uranium exposures contribute a small amount to the collective dose are excluded from this review because their exposure was primarily to radiological hazards (e.g. external exposure to γ-radiation or internal exposure to plutonium), which are covered in separate sections of this *Monograph*, and not repeated here.

(a) Occupational studies

Interpretations of occupational cohort analyses based upon external comparisons, in which mortality in a worker population is compared to mortality in an referent population by calculation of SMRs, are complicated by potential bias due to health-related selection into employment (sometimes referred to as the healthy worker hire effect). In addition, SMR analyses are often conducted in settings in which the investigator lacks quantitative exposure estimates. Such analyses may combine together a small subgroup of workers with substantial potential for uranium exposure with a larger group of people who had little or no uranium exposure; consequently, these studies often have limited ability to detect the potential adverse effects of uranium exposures. Where available, this review gives greater attention to occupational cohort analyses that are based upon internal comparisons, in which workers' exposures were quantified permitting comparisons between worker groups with different exposure histories. However, quantifications of internal and external radiation doses from uranium in occupational cohort studies are often accompanied with substantial uncertainty. Therefore, the interpretation of study results based upon contrasts drawn between workers with different levels of uranium exposure may be complicated by bias to errors in exposure estimation (see Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.14.pdf).

External exposure to penetrating forms of ionizing radiation may result in whole-body irradiation. In contrast, examination of the effects of internal exposure to uranium typically focuses on the organ systems through which uranium particles pass. Inhalation is a primary route of exposure to uranium in many occupational settings, leading to interest in lung cancer and cancers of the upper aerodigestive tract. Urinary tract and haemato- and lymphopoietic cancers have also been of interest because insoluble uranium may deposit in nodes, and soluble uranium compounds are transported by the blood to the kidney for excretion.

(i) Uranium millers

Three cohort studies of US uranium millers have been reported since the previous *IARC Monograph*; all report on the analysis of SMRs. [The Working Group noted that it is likely that two of the studies (Boice *et al.*, 2007, 2008) were partly included in the pooled analyses by Pinkerton *et al.* (2004). Due to different follow-up periods for those studies, it was impossible to quantify the exact extent of overlap.] Although in all three cohort studies mortality from all causes was less than expected (based upon comparisons

to US mortality rates), in two of the three studies, a non-significant excess of lung cancer mortality was reported (Pinkerton *et al.*, 2004; Boice *et al.*, 2007), as well as excesses of lymphatic and haematopoietic cancers other than leukaemia in the largest of the cohort studies (Pinkerton *et al.*, 2004). In that study, which was a pooled study of seven uranium miller cohorts, a significant excess of lung cancer mortality was observed in analyses using state mortality rates as a comparison (SMR, 1.51; 95%CI: 1.19–1.89). Potential confounding by smoking, silica exposure, or other occupational hazards complicated the interpretation of these results, and these studies lacked a direct measure of cumulative exposure to uranium.

(ii) Uranium enrichment and fabrication workers

Since the previous *IARC Monograph*, three studies have been reported on mortality among workers at US uranium enrichment and fabrication plants (see Table 2.14 on-line). The Mallinckrodt Chemical Works at St. Louis, Missouri, processed tonnage quantities of uranium ore into pure uranium tetrafluoride and metal. Dupree-Ellis *et al.* (2000) estimated the effects of external radiation on cancer mortality among workers at this facility. All-cause mortality was significantly lower than expected based upon national rates (SMR, 0.90; 95%CI: 0.85–0.96), and SMRs were 1.05 (95%CI: 0.93–1.17) for all cancers, and 1.17 (95%CI: 0.54–2.18) for kidney cancer mortality. There was a positive dose–response relationship between kidney cancer and external radiation; the ERR/Sv for kidney cancer was 10.5 (90%CI: 0.6–57.4). Seven men who died of kidney cancer had worked in the pitchblende processing area, where external radiation exposure was potentially high because most operations were done manually.

The US Department of Energy's Y-12 facility, located in Oak Ridge, Tennessee, operated as a uranium enrichment facility, and later as a facility for fabrication of nuclear weapons parts, and recycling and recovery of uranium and other radioactive materials. A study of Y-12 workers examined associations between external and internal radiation dose and lung cancer mortality (Richardson & Wing, 2006). Internal exposure to ionizing radiation was primarily in the form of α-particle radiation from uranium isotopes, with the primary route of exposure being inhalation of uranium dust. Cumulative external radiation dose (under a 5-year lag) was positively associated with lung cancer mortality; cumulative internal radiation dose exhibited little evidence of association with lung cancer mortality.

The US Department of Energy's Portsmouth Gaseous Diffusion facility, located in Piketon, Ohio, operated as a uranium enrichment facility. A nested case–control analysis was conducted to examine associations between mortality from several cancers, including lung cancer, and external dose; no significant association was observed (Ahrenholz *et al.*, 2001).

Two studies have been reported on mortality among workers at fuel fabrication and uranium production facilities in the United Kingdom (see Table 2.14 on-line). McGeoghegan & Binks (2000b) reported on the association between external radiation dose and mortality among workers employed at the Springfields Uranium Production Facility. No estimates of internal exposure to uranium were used in this study. [The Working Group noted that with respect to incidence, a positive association between all cancers (including or excluding leukaemias) and cumulative external radiation dose under a 20-year lag was observed; this was largely due to the positive association between cumulative external radiation dose and incidence of lung cancer (trend statistic, 1.72; $P < 0.05$) and all lymphatic and haemopoetic cancers (trend statistic, 2.30; $P < 0.05$).] A follow-up study of a cohort of workers at the Capenhurst plant (the primary activity of which was enrichment of uranium) was also carried out, (McGeoghegan

& Binks, 2000a). A positive association was observed between bladder cancer incidence and cumulative external radiation exposure under a 20-year lag (trend statistic, 1.95; $P = 0.035$).

Baysson *et al.* (2000) reported on mortality among 356 workers employed in the metallurgy department of the French Atomic Energy Commissariat. Job and hazard forms were used to derive qualitative hazard assessments for 30 products. The risk of all-cancer mortality appeared to increase with increasing duration of exposure to radionuclides and chemical; given the small numbers of events, dose–response associations were not estimated for other outcomes.

(iii) Depleted uranium

During the manufacture of nuclear fuel for most types of reactors, the relative concentration of isotopes with higher radioactivity is increased. A by-product of this enrichment process is depleted uranium. Consequently, depleted uranium is constituted of the same three isotopes as natural uranium, but with lower relative concentrations of ^{235}U and ^{234}U. Radiotoxicity of natural uranium is 60% higher than that of depleted uranium, while their chemotoxicity is similar (Bleise *et al.*, 2003).

Cohort studies of Swedish and Danish soldiers deployed to the Balkans have been reported (Gustavsson *et al.*, 2004; Storm *et al.*, 2006) with follow-up for cancer incidence. Most persons were deployed for short periods (e.g. 6 months), and no uranium exposures were quantified (see Table 2.14 on-line). Among soldiers in the Swedish cohort (Gustavsson *et al.*, 2004), cancer incidence was slightly higher than expected (SIR, 1.2; 95%CI: 0.9–1.7). There was no excess of lung cancer (one case observed versus 0.8 expected in men, and one case observed versus 0.1 expected in women), but there were eight cases of testicular cancer versus 4.6 expected (SIR, 1.9; 95%CI: 0.8–3.7). Among Danish soldiers deployed to the Balkans (Storm *et al.*, 2006), cancer incidence was slightly lower than expected among male soldiers (SIR, 0.9; 95%CI: 0.7–1.1, based on 84 cases) and slightly higher than expected among female soldiers (SIR, 1.7; 95%CI: 0.9–3.0, based on 12 cases). Bone cancers were in excess among men (SIR, 6.0; 95%CI: 1.6–15.3, based on four cases).

Kang & Bullman (2001) reported results from a follow-up study on mortality of a cohort of 621902 US Gulf War veterans who arrived in the Persian Gulf before May 1, 1991, and a cohort of 746248 US non-Gulf veterans. Follow-up for mortality was conducted through 1997. Male Gulf War veterans had a slightly lower all-cause mortality rate than non-Gulf veterans (RR, 0.95; 95%CI: 0.92–0.99), and female Gulf War veterans had a slightly higher all-cause mortality rate than non-Gulf veterans (RR, 1.16; 95%CI: 0.97–1.38). Male Gulf War veterans also had a slightly lower all-cancer mortality rate than non-Gulf veterans (RR, 0.90; 95%CI: 0.81–1.01), and female Gulf War veterans had a slightly higher all-cancer mortality rate than non-Gulf veterans (RR, 1.11; 95%CI: 0.78–1.57). A potential limitation of the study was that some of the non-Gulf War veterans may have been less healthy than the veterans sent to the Persian Gulf.

Macfarlane *et al.* (2003) examined cancer incidence rates in a cohort of 51721 United Kingdom Gulf war veterans and 50755 service personnel matched for age, sex, rank, service, and level of fitness who were not deployed in the Gulf. Cancer incidence was ascertained over the period up from 1 April 1991 (the end of the Gulf war) to 31 July 2002. Incidence rate ratios (IRR) were calculated comparing these two groups. There was no excess in all cancers or lung cancer among the Gulf cohort; non-significant excesses were observed for several cancer sites, including lymphoid and haematopoietic cancers (IRR, 1.30; 95%CI: 0.83–2.03), urinary tract cancers (IRR, 1.42; 95%CI: 0.61–3.32), and upper digestive tract cancers (IRR, 1.47; 95%CI: 0.53–4.14). Self-reported information was collected via surveys on exposure to potentially hazardous materials,

including depleted uranium. Among the Gulf veterans who participated in at least one of the surveys, reported exposure to depleted uranium was not associated with an excess risk of cancer overall (IRR, 0.63; 95%CI: 0.30–1.36). Macfarlane *et al.* (2005) examined cause-specific mortality in the above study. There was no overall difference in the death rates between cohorts or in malignant causes of death. Reported exposure to depleted uranium was uncommon among those deployed (7%). There was a non-significant increased risk of death among those who reported exposure (mortality rate ratio, 1.48; 95%CI: 0.83–2.64). The small proportion of Gulf Veterans who reported exposure to depleted uranium experienced a doubling in the risk of dying from non-external causes, although, again, the result was not statistically significant (mortality rate ratio, 1.99; 95%CI: 0.98–4.04). Of the nine people who reported exposure to depleted uranium and who died from a disease-related cause, seven were from cancer: three malignant cancers of the oesophagus, three malignant cancers of the brain, and one cancer of the brain of uncertain behaviour (benign/malignant).

(b) Synthesis

Uranium creates a relatively complex spectrum of radiological hazards, including external exposure to β-particles and γ-radiation, and internal exposures to α-particles, β-particles, and γ-radiation. The available epidemiological studies of the effects of internal exposure to uranium have been constrained by limitations of available historical records from routine monitoring for uranium intakes. Consistent with the evidence from studies of the distribution of uranium in humans after intakes of insoluble compounds, excesses of mortality from respiratory and lymphatic cancers have been reported in some studies of uranium millers. SMR analyses of data pooled for seven uranium miller cohorts (excluding workers known to have been employed in uranium mining) in Colorado reported excesses of lung cancer and lymphatic cancers. An excess of lung cancer mortality also was observed among the 450 uranium mill workers in the Uravan cohort. No excess of lung cancer was reported among the uranium mill workers in the Grants cohort, although excess mortality due to kidney and bladder cancer was reported in that cohort.

Several studies have quantified radiation doses among uranium-processing workers. External doses tended to be better quantified than internal doses from uranium intakes. Limitations in quantifying internal doses from uranium reflect the limitations of historical records (e.g. records were typically not available for all workers over all periods of employment), and the limitations of historical bioassay programmes for the reconstruction of internal dose estimates. Evidence of positive associations between cumulative external dose and lung cancer have been reported among workers at the Y-12 facility, and among workers at the Springfields facility, but not among workers at the Capenhurst, Mallinckrodt, or Portsmouth facilities. The magnitudes of external doses were quite low at these facilities, limiting the statistical power of such investigations. Internal doses from uranium were not associated with lung cancer mortality in analyses of the Y-12 cohort. A small study of workers employed by the French Atomic Energy Commissariat suggested an association between duration of exposure to radionuclides and all-cancer mortality.

Epidemiological studies of cancer incidence or mortality among soldiers with potential exposure to depleted uranium have used little or no quantitative assessment of exposure magnitude, which poses serious limitations in these studies of the health effects of presumably low-level exposures to uranium.

Overall, two epidemiological cohort studies of uranium enrichment workers reported significant positive associations between the radiation dose quantified by personal dosimeters and

lung cancer (McGeoghegan & Binks, 2000b; Richardson & Wing, 2006). Lung cancer risk could be caused either by external exposure to γ-radiation, or by α-particles emitted by uranium particles inhaled into the lung, or both. In addition, an excess of lung cancer mortality was observed in cohorts of mortality among uranium millers. However, these associations are not consistent across all studies, and there is the potential for confounding of these associations by smoking as well as occupational hazards other than uranium.

3. Cancer in Experimental Animals

3.1 Previous *IARC Monograph*

The carcinogenic risks to humans from internally deposited radionuclides have been reviewed by previous IARC Working Groups (IARC, 1972, 1987, 1988, 2001). Alpha-emitters have been tested for carcinogenicity at various doses and under various conditions in mice, rats, hamsters and dogs.

3.1.1 Radon-222

^{222}Rn induced respiratory tract cancers in rats (Perraud *et al.*, 1972), and lung epidermoid carcinoma, bronchioalveolar carcinoma, and nasal mucosa squamous carcinoma, in dogs by inhalation (Cross *et al.*, 1982).

3.1.2 Polonium-210

^{210}Po induced lung adenocarcinomas in hamsters by intratracheal instillation (Little *et al.*, 1978).

3.1.3 Radium-224

^{224}Ra induced osteogenic sarcomas (Luz *et al.*, 1979; Müller *et al.*, 1983) and myeloid leukaemia (Humphreys *et al.*, 1993) in mice by intraperitoneal injection. ^{224}Ra induced osteosarcomas and nasal mucosa tumours in dogs when administered by intravenous injection (Muggenburg *et al.*, 1995, 1996).

3.1.4 Radium-226

^{226}Ra induced bone sarcomas in mice by intraperitoneal injection (Taylor *et al.*, 1983), and bone sarcomas and intraocular melanomas in dogs by intravenous injection (Taylor *et al.* 1972, 1997, 2000; Lloyd *et al.* 1993, 1994a).

3.1.5 Thorium-228

^{228}Th caused osteosarcomas in dogs by intravenous injection (Mays *et al.*, 1987; Lloyd *et al.*, 1997a).

3.1.6 Thorium-230

^{230}Th in a colloidal form caused liver cancer in rats (Wesch *et al.*, 1983) and mice (Taylor *et al.*, 1993).

3.1.7 Thorium-232

^{232}Th induced hepatocellular carcinomas in hamsters by intravenous injection (Guilmette *et al.*, 1989), and liver carcinomas, intrahepatic bile-duct carcinomas and haemangiosarcomas in rats by intravenous injection (Wegener *et al.*, 1983; Wesch *et al.*, 1983).

3.1.8 Uranium

Uranium ore dust containing 44% elemental uranium induced bronchioalveolar carcinomas, bronchial carcinomas and squamous cell carcinomas in rats by inhalation (Mitchel *et al.*, 1999). An incidence of osteosarcomas (2%) was reported by Ellender *et al.* (2001) after intraperitoneal injection of uranium in mice.

3.1.9 Neptunium-237

^{237}Np induced osteosarcomas in rats when administered by intravenous injection (Sontag *et al.*, 1997), and adenocarcinomas and squamous cell carcinomas of the lung by inhalation (nose-only) exposure (Dudoignon *et al.*, 1999).

3.1.10 Plutonium-238

^{238}Pu caused lung cancer in hamsters by inhalation (Thomas & Smith, 1979), and caused lung, liver and bone cancers in dogs exposed by inhalation (Gillett *et al.*, 1988; Park *et al.*, 1997).

3.1.11 Plutonium-239

^{239}Pu caused liver, lung and bone cancers in dogs by inhalation (Dagle *et al.*, 1996; Hahn *et al.*, 1999). In mice (Taylor *et al.*, 1981; Svoboda *et al.*, 1982; Humphreys *et al.*, 1987; Oghiso *et al.*, 1994, 1997; Oghiso & Yamada, 1999), hamsters (Brooks *et al.*, 1983) and dogs (Lloyd *et al.*, 1993, 1994b) exposed to ^{239}Pu by parenteral administration, bone and liver cancers were observed; haematopoietic cancers were also observed in mice (Svoboda *et al.*, 1982).

3.1.12 Americium-241

^{241}Am induced osteoblastic osteosarcomas of the skeleton and lymphoreticular system (lymphomas and lymphosarcomas) in 314 CBA mice (Nilsson & Broomé-Karlsson, 1976) when administered by intraperitoneal injection. ^{241}Am increased the incidence of osteosarcomas in mice by intravenous injection (van den Heuvel *et al.*, 1995), and induced bile-duct adenomas and carcinomas, fibrosarcomas and haemangiosarcomas in both deer mice and grasshopper mice by intraperitoneal injection (Taylor *et al.*, 1986). Osteosarcomas were induced and one leukaemia was reported in August/Marshall hybrid rats after intravenous injection (Taylor, 1986). Osteoblastic osteosarcomas developed in dogs after inhalation of a monodisperse ^{241}Am aerosol (Gillett *et al.*, 1985).

3.1.13 Curium-244

Skeletal cancers were observed in rats exposed by intravenous injection (Taylor, 1986) to ^{244}Cm, and lung and liver cancers in rats exposed by inhalation (Sanders & Mahaffey, 1978; Lundgren *et al.*, 1997).

3.1.14 Californium-249 and californium-252

Skeletal cancers were observed in mice given ^{249}Cf or ^{252}Cf intraperitoneally (Taylor *et al.*, 1983), and in dogs treated intravenously (Lloyd *et al.*, 1994c).

3.2 Studies published since the previous *IARC Monograph*

Table 3.1 summarizes published studies that relate to the measurement of radiation-induced cancer from incorporated α-particle emitters in experimental animals. Also included are references that were omitted from the previous *IARC Monograph*, but considered important to include here.

In all of the studies in Table 3.1, at least one target tissue or organ was shown to have a statistically significant increase in the incidence of cancer that could be attributed to the incorporated radionuclide. Typically, the target organ receiving the largest dose incurred the formation of tumours.

3.2.1 Radon-222

(a) Rat

Using significant numbers of animals exposed to ^{222}Rn and progeny, both Monchaux & Morlier (2002) and Collier *et al.* (2005) investigated the interplay between total exposure and exposure rate for chronic inhalation of ^{222}Rn and progeny

Table 3.1 Studies in experimental animals exposed to radionuclides internally deposited

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Polonium-210				
Syrian hamsters (M) Lifespan Little *et al.* (1985), Shami *et al.* (1982)	Intratracheal instillation ^{210}Po carrier-free	Lung:	Statistical analysis of difference between groups (P 0.02–0.05)	
	2.4 Gy at 16 mGy/d (120 d average to deliver 80%)	14/62 (23%)		
	2.4 Gy at 32 mGy/d (60 d of dose)	15/69 (25%)		
	2.4 Gy at 192 mGy/d (10 d of dose)	26/58 (45%)		
	once/wk for 15 wk			
	1 ^{210}Po instillation only	2/41 (5%)		
	Control	0		
	240 mGy at 1.6 mGy over 120 d, 15 instillations	6/68 (9%)		
	240 mGy at 19 mGy, 1 instillation over 10 d	1/85 (1%)		
	saline only instillation	0		
	Animals/group at start (NR)			
Radon-222				
Rat, Sprague Dawley (M) 1–12 mo Monchaux & Morlier (2002)	Chronic inhalation ^{222}Rn and progeny: Groups: 1 (105 WLM, 188 WL); 2 (107, 147); 3 (100, 58); 4 (100, 13); 5 (100, 152); 6 (42,18); Controls	Lung (malignant tumours, %): 7.1, 2.8, 4.2, 5.4, 1.6[a], 1.2[a], 0.6	Data combined from CEA & AEA-Technologies studies.	
	Group 0: 120 unexposed controls Group 00: 120 sham-exposed controls 785 historical controls; 120–240 exposed animals/group	No lung cancer was observed in controls	[a] Not statistically different from controls	
Rat, Sprague Dawley (M) Lifespan Collier *et al.* (2005)	Chronic inhalation, ^{222}Rn and progeny (attached fraction > 98.5%)	Lung (primary tumours):		
	Study 1 (1000 WL): 200, 400, 800, 1 600, 3 200 WLM	Study 1–8/156 (5%); 1/111 (1%); 2/97 (2%); 8/102 (8%); 6/34 (18%)	$P < 0.005$	
	Study 2 (1000 WLM): 250, 500, 1 000, 2000 WL	Study 2–8/46 (17%); 3/46 (6.5%); 7/46 (15%); 11/52 (21%)	$P < 0.005$	
	Study 3 (100 WLM): 15, 150, 1 000 WL	Study 3–5/190 (3%); 6/186 (3%); 3/182 (2%); 4/82 (2%)	$P < 0.05$	
	46–190 animals/group			

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Radium isotopes				
Dog, beagle (M, F) Lifespan Lloyd *et al.* (2000a)	i.v. injection $^{226}RaCl_2$.: 0.275, 0.651, 2.31, 6.13, 12.5, 39.6, 119, 383 kBq/kg; 1 × at 1.5 yr 10–25 animals/group	Osteosarcomas: 0/10; 2/25 (8%); 2/23 (8.7%); 1/14 (7.1%); 5/13 (38.5%); 11/12 (91.7%); 12/13 (92.3%); 9/10 (90%)	$P < 0.2$	
	i.v. injection $^{228}RaCl_2$.: 0.656, 1.83, 5.68, 11.1, 34.5, 96.8, 306 kBq/kg; 1x at 1.5 yr 7–13 animals/group	Osteosarcomas: 0/12; 1/13 (7.7%); 10/12 (83.3%); 9/12 (75%); 12/12 (100%); 6/8 (75%); 1/7 (14%)	$P < 0.2$	
Dog, beagle (M, F) Lifespan Taylor *et al.* (2000)	i.v. injection, single $^{226}RaCl_2$. Dose to intraocular melanotic tissue, Gy 0; 0.93; 2.23; 5.59; 7.08; 21.01; 31.58; 67.47 9–25 animals/group; 132 controls	Intraocular melanomas: 1/132 (1%); 1/25 (4%); 3/22 (14%); 5/12 (42%); 1/12 (6%)		
Thorium-228				
Dog, beagle (M, F) Lifespan Lloyd *et al.* (2000a)	i.v. injection ^{228}Th citrate. 0.063, 0.192, 0.560, 1.12, 3.40, 10.7, 31.8, 99.7 kBq/kg; 1 × at 1.5 yr 2–13 animals/group	Osteosarcomas 0/13; 1/12 (8.3%); 5/12 (41%); 11/13 (77%); 12/12 (100%); 12/12 (100%); 2/4 (50%)	$P < 0.2$	
Thorium-232 (Thorostrast)				
Rat, Wistar (M) Lifespan Hahn *et al.* (2002)	i.m. implantation, $^{232}ThO_2$ (Thorotrast) 2 × (0.05 mL, 25% suspension), 2 injections 50 animals/group	Soft-tissue wound site tumours: 0; 25/50 (50%)	Th vs DU $P < 0.0014$	
Depleted uranium				
Rat, Wistar (M) Lifespan Hahn *et al.* (2002)	IM implantation, DU metal. Groups: Surgical control; Tantalum metal (5 × 5 × 1.1mm) wafer implant control; DU (1mm x 2mm) 4 pellets; DU (2.5 × 2.5 × 1.5mm) 4 wafers; DU (5 × 5 × 1.5mm) 4 wafers 50 animals/group	Soft-tissue wound site tumours: 0; 2/50 (4%); 0; 3/50 (6%); 9/49 (18%) Kidney tumours: 0; 0; 1/50 (2%); 1/50 (2%); 2/49 (4%)	Incidence of kidney tumour considered equivocal Th > DU 5.0 × 5.0mm; $P < 0.0014$ DU 5.0 × 5.0mm > sham cont.; $P = 0.0012$ DU 5.0 × 5.0mm > Ta; $P < 0.0028$	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Uranium citrate				
Mouse, CBA/H (M) Ellender *et al.* (2001)	Multiple i.p. injections (9 over 3 wk) ^{233}U citrate (average bone doses calculated to 500 days after administration) 0; 0.2-0.3; 0.5-1.0; 1.3-1.6 Gy; 50–100 animals/group; 100 controls	Osteosarcomas: 2/88 (2%); 2/91 (2%); 1/54 (2%); 1/48 (2%) Myeloid leukaemia: 0; 4/91 (4%); 2/54 (4%); 2/48 (4%) Hepatocellular carcinomas: 38/88 (43%); 52/91 (57%); 29/54 (54%); 26/48 (54%)		
Neptunium-237				
Rat, Sprague Dawley (M) Lifespan Dudoignon *et al.* (2001)	795 controls; 109 controls from a previous study Single inhalation (nose-only), $^{237}NpO_2$. ILD groups (Bq): 0, 90, 190, 740, 1 480, 2 560, 4 070. Corresponding mean lung doses (Gy). 0, 0.5, 1.1, 4.1, 7.7, 14.5, 36.4 12–102 animals/group	Lung tumour incidence* (% rats with tumours): 0.6, 17.6, 23.5, 62.6; 66.7, 75.0, 91.7		Mean survival (SD) d 778 (109), 735 (130), 748 (129), 725 (117), 727 (119), 698 (109), 627 (92). *Scoring included neoplastic and preneoplastic lesions
Rat, Sprague Dawley (M) Lifespan Dudoignon *et al.* (2003)	Single inhalation $^{237}NpO_2$. Mean dose Gy(sd): 0, 0.5 (0.1), 1.1, (0.3), 4.1 (0.9), 7.7 (1.4), 14.5 (3.3), 36.4 (10.2) 12–102 animals/group; 785 controls; 109 controls from a previous study	Lung carcinoma incidence: 5/785 (0.6%); 1/33 (3%); 7/102 (7%); 8/24 (33%); 9/23 (39%); 23/24 (96%); 18/12 (150%)		Animals with > 1 tumour Experimental study same as Dudoignon *et al.* (2001) except with complete histopathology
Plutonium oxide				
Rat, Sprague Dawley (M) Lifespan Dudoignon *et al.* (2003)	Single inhalation $^{239}PuO_2$. ILD groups (Bq): 0, 410, 600, 810, 1310, 2230, 3450. Corresponding mean lung doses (Gy). 0, 2.5, 3.6, 5.0, 8.2, 14.0, 22.5 26–31 animals/group; 795 controls, 109 controls from previous studies	Lung carcinoma incidence: 5/795 (0.6%); 2/30 (7%); 2/28 (7%); 3/31 (10%); 8/35 (23%); 7/26 (27%); 10/26 (38%)		Mean survival (SD) Scoring included neoplastic and preneoplastic lesions 778 (109), 796 (119), 756 (167), 788 (128), 768 (123), 731 (147), 754 (133) Animals with > 1 tumour Experimental study same as Dudoignon *et al.* (2001) except with complete histopathology

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (F) Lifespan Oghiso & Yamada (2003a)	Inhalation, single, $^{239}PuO_2$, lung dose Gy (SD): 0; 0.16(0.05), 0.45(0.24), 1.59(0.32), 2.76(0.43), 4.76(0.24), 5.43(0.29), 6.61(0.28), 8.52(0.67) 30–134 animals/group; 206 controls	Lung (malignant tumour): 1/206 (0.5%); 1/80 (1.2%); 12/134 (9%); 60/128 (47%); 78/126 (62%); 32/40 (80%); 27/31 (87%); 28/31 (90%); 27/30 (90%)	$P < 0.001$	
Dog, beagle, young adult (M, F) Lifespan Muggenburg *et al.* (2008)	Single Inhalation, $^{239}PuO_2$ monodisperse aerosols (0.75,1.5, 3.0 μm AMAD). Exposure groups (median ILB, kBq ^{239}Pu lung burden/kg body mass): 0, 0.16, 0.63, 1.6, 3.7, 6.4, 14, 29. Lung doses to death depend on particle size group 10–21 animals/sex/group; 18 controls/sex/group; 142 controls from a previous study	Lung (tumours): 4/36 (11%); 8/21 (38%); 25/37 (68%); 39/42 (93%); 29/33 (88%); 20/31 (65%); 4/27 (15%); 0		Median age at death (d) 4865, 4637, 3152, 2079, 1413
Plutonium citrate				
Mouse C3H/HeN, C57BL/6J, $B6C3F_1$ (F) Lifespan Oghiso & Yamada (2003b)	Single IP injection ^{239}Pu citrate. Injected dose (kBq). C3H: 0, 0.1, 0.5, 1.0, 5.0, 10.0 C57BL/6: 0, 0.1, 0.5, 1.0, 5.0, 10.0 $B6C3F_1$: 0, 0.1, 0.5, 1.0, 5.0, 10.0 30–60 animals/group	Osteosarcomas incidence (%): 0; 4/30 (13.3%); 19/30 (63.3%); 14/30 (46.7%); 15/32 (46.9%); 8/30 (26.7%) 0; 3/30 (10%); 7/31 (22.6%); 16/32 (50%); 12/31 (38.7%); 4/30 (13.3%) 0; 8/31 (25.8%); 17/33 (51.5%); 12/33 (36.4%); 10/32 (31.2%); 11/32 (34.4%)	$P < 0.001$	
Mouse, C3H, C57BL/6, $BC3F_1$ (F) Lifespan Oghiso & Yamada (2000)	Single IP injection. ^{239}Pu citrate. Skeleton doses to death Gy (SD) C3H mice: 0, 0.68(0.04), 2.71(0.36), 4.42(0.58), 16.3(2.1) C57BL/6: 0, 0.63(0.06), 2.66(0.43), 4.08(0.69), 18.3(2.0) $B6C3F_1$: 0, 0.63(0.06), 2.62(0.37), 4.38(0.51), 16.8(1.8) 30–60 animals/group	Osteosarcomas incidence (%): C3H–0; 7/30 (23.3%); 19/30 (63.3%); 14/30 (46.7%); 12/30 (40%) C57BL/6–0; 4/30 (13.3%); 7/30 (23.3%); 16/30 (53.3%); 20/30 (66.7%) $BC3F_1$–1/60 (1.7%); 9/30 (30%); 17/30 (56.7%); 13/30 (43.3%); 10/30 (33.3%)		

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Dog, beagle (M, F) Lifespan Lloyd *et al.* (2001)	i.v. injection ^{239}Pu citrate. Dose groups (kBq/kg body mass): 0, 0.026, 0.067, 0.201, 0.382, 0.576, 1.77, 3.52, 11.0, 33.6, 106 8–46; 132 controls	Osteosarcoma incidence: 1/132 (1%); 1/28 (4%); 2/46 (4%); 4/38 (10%); 8/38 (21%); 10/26 (38%); 10/14 (71%); 10/12 (83%); 12/12 (100%); 12/12 (100%); 7/8 (87%)		
Plutonium nitrate				
Mouse, CBA/H (M) Lifespan Ellender *et al.* (2001)	Multiple i.p. injections (9 over 3 wk) ^{239}Pu citrate. Dose groups (Gy to 500 d). 0, 0.2, 0.5, 1.3 50–100 animals/group	Osteosarcoma incidence: 2/88 (2%); 2/97 (2%); 6/55 (11%); 18/124 (15%): Myeloid leukaemia 0; 4/97 (4%); 3/55 (6%); 11/124 (9%) Hepatocellular carcinomas: 38/88 (43%); 55/97 (60%); 43/55 (78%); 72/124 (58%)	$P < 0.001$	
Americium citrate				
Mouse, CBA/H (M) Lifespan Ellender *et al.* (2001)	Multiple i.p. injections (9 over 3 wk) ^{241}Am citrate. Dose groups (Gy to 500 d). 0, 0.3, 0.9, 1.6 at 12 wk 50–100 animals/group	Osteosarcoma incidence: 2/88 (2%); 0; 4/143 (3%); 10/48 (21%) Myeloid leukaemia: 0; 4/93 (4%); 12/143 (8%); 5/48 (10%) Hepatocellular carcinomas: 38/88 (43%); 45/93 (48%); 90/143 (63%); 36/48 (75%)	$P < 0.001$	
Curium–242				
Mouse, CBA/Ca (F) Lifespan Priest *et al.* (2006)	Inhalation single ^{242}Cm in FAP. Mean dose to lung Gy (5%, 95% CI) 120–160 animals/group 0, A1: 0.55(0.37–0.76); A2: 1.55(1.04–2.15); A3: 2.67(1.79–3.70); A4: 4.69(3.15–6.49)	Lung (malignant tumours): 105/371 (28%); 44/111 (40%); 49/113 (44%); 55/100 (55%); 58/112 (52%)	A1 vs control $P < 0.05$ A3 vs control $P < 0.05$	

AMAD, activity median aerodynamic diameter; CI, confidence interval; d, day or days; DU, depleted uranium; F, female; FAP, fused aluminosilicate particle; ILB, initial lung burden; ILD, initial lung deposit; i.m., intramuscular; i.p., intraperitoneal; i.t., intratracheal; i.v., intravenous; M, male; mo, month or months; NR, not reported; Ta, tantalum; vs, versus; wk, week or weeks; yr, year or years

in non-smoking rats. The results of both studies, plus previous data from other experiments, were consistent in demonstrating that for high cumulative exposures (about 1000 WLM), the tumour risk increases with increased exposure duration, and therefore decreased exposure rate (the so-called inverse dose–rate effect). However, for low cumulative exposure (> 100 WLM), increased exposure duration or decreased exposure rate decreased lung cancer risk. This biphasic response is important to consider when applying data from high exposure rate populations (such as some of the uranium miner cohorts) to low exposure rate groups (exposure in indoor environments).

3.2.2 Polonium-210

(a) Hamster

By varying the number of repeated intratracheal instillations that contained ^{210}Po, Little *et al.* (1985) were able to show that frank malignant lung tumour incidence increased with increasing dose rate. All groups received the same total dose to the lung (Table 3.1). For these groups, the total number of instillations was kept constant by substituting instillation of equal volumes of isotonic saline when no ^{210}Po was administered. Of significant note was the decreased tumour incidence for a group in which a single ^{210}Po instillation was administered without accompanying saline instillations. This result reinforced the conclusions of Shami *et al.* (1982) who demonstrated the importance of the saline administrations given after ^{210}Po in increasing lung tumour incidence.

3.2.3 Radium isotopes

(a) Dog

The study results on osteosarcomas induced by ^{226}Ra in dogs shown in Table 3.1 and reported by Lloyd *et al.* (2000a) are similar but not identical to those previously published by the same authors in 1993 (different number of study animals, different percentage incidence values). However, the differences do not affect the interpretation of the results, i.e. that the dose–response for osteosarcoma induction for ^{226}Ra is a linear response over the study dose range (Lloyd *et al.*, 1993). The bone cancer data for intravenous ^{228}Ra in dogs (Lloyd *et al.*, 2000a) appeared to be new, but the authors did not analyse the dose–response relationship. However, in an earlier paper, Lloyd *et al.* (1997a) concluded that for equal skeletal radiation doses, ^{228}Ra would produce twice as many osteosarcomas as would ^{226}Ra, i.e. a toxicity ratio of 2.

Additionally, Taylor *et al.* (2000) showed that intravenous ^{226}Ra in dogs resulted in an increased incidence of eye melanoma. The incidence was monotonically dose-related over a range of 0.9–5.6 Gy (dose to intraocular melanotic tissue), but decreased with higher doses so that at 21 Gy and above, no melanomas were observed.

3.2.4 Thorium-228

(a) Dog

The study results on osteosarcoma incidence induced by ^{228}Th in dogs shown in Table 3.1 and reported in Lloyd *et al.* (2000a) are essentially identical to the results previously published by Mays *et al.* (1987). The toxicity ratio for ^{228}Th compared with ^{226}Ra is 8.5 (Lloyd *et al.*, 1997b), which is similar to that of its first progeny ^{224}Ra (toxicity ratio of 6 for single injection, 16 for repeated administration).

3.2.5 Thorium-232 (Thorostrast)

(a) Rat

Hahn *et al.* (2002) used an intramuscularly implanted Thorotrast suspension as a positive tumour control for their study of the carcinogenicity of depleted uranium metal fragments in rats. Thorotrast has been known to cause granulomas in humans when the Thorotrast extravasated from the intravenous injection site,

and infiltrated local soft tissue (Dahlgren, 1967; Liebermann *et al.*, 1995). A single dosage of 0.05 mL of a 25% suspension of Thorotrast injected into each biceps femoris of rats induced a 50% lifetime soft-tissue tumour incidence (Hahn *et al.*, 2002).

3.2.6 Depleted uranium

(a) Rat

Hahn *et al.* (2002) reported that intramuscular implantation of depleted uranium pellets in rats produced malignant soft-tissue tumours (fibrous histiocytoma, fibrosarcoma, osteosarcoma, in decreasing order) at the site of implantation, and with incidence that increased with increasing size of the implant. The dose–response relationship could not be directly linked to the radiation dose from uranium because of the confounding from varying implant sizes as well as varying amounts of uranium corrosion products at the implant site. No other significant cancers were found.

3.2.7 Neptunium-237

(a) Rat

Dudoignon *et al.* (2001, 2003) measured the incidence of lung cancer in rats that received a single inhalation exposure to respirable $^{237}NpO_2$ aerosols. Against radiation dose to the lung, the incidence of cancer had a linear dose–response from 0.5 to 36 Gy, and the relative effectiveness for producing lung cancer per unit dose was 3.3 times greater for neptunium than it was for plutonium.

3.2.8 Plutonium-239

(a) Plutonium Oxide ($^{239}PuO_2$)

(i) Rat

Dudoignon *et al.* (2001, 2003) measured the incidence of lung cancer in rats that received a single inhalation exposure to $^{239}PuO_2$. The incidence of cancer had a linear dose–response from 2.5 to 22 Gy.

Oghiso & Yamada (2003a) exposed rats by inhalation to polydisperse $^{239}PuO_2$ aerosols and followed the animals for lifespan. Their results showed dose-dependent survival reduction that was correlated with increased malignant lung tumours at doses over 0.45 Gy, reaching a maximum incidence of 90% at 6.6–8.5 Gy. They also noted that the relative effectiveness for 50% lung carcinoma incidence was about 11 times higher than for single thoracic irradiation with X-rays.

(ii) Dog

In an experiment designed to study the "hot particle hypothesis" for inhaled α-particle emitting radionuclides, Muggenburg *et al.* (2008) exposed dogs by single inhalation to monodisperse aerosols of $^{239}PuO_2$ of three different particle sizes (0.75, 1.5, 3.0 μm Activity Median Aerodynamic Diameter). In so doing, the relationships between average dose and dose rate to the lung could be compared to local dose rate around each plutonium particle, and the fraction of lung tissue irradiated. Based on the lung doses achieved in the study, which ranged from about 1 to 60 Gy, significant incidences of lung cancer were observed for all particle size groups, and there were good dose–response relationships. Comparison of the particle-size-specific groups indicated that a more uniform distribution of α-particle radiation dose within the lung had an equal or possible greater risk of neoplasia than less uniform distributions of radiation dose. These results are consistent with those from other

studies in which the uniformity of α-particle radiation dose was also compared.

(b) Plutonium Citrate (^{239}Pu Citrate)

(i) Mouse

Oghiso & Yamada (2003b) compared the bone tumour incidences for three strains of mice (C3H/He, C57BL/6, B6C3F$_1$) injected with varying doses of ^{239}Pu Citrate, and found that the dose–response patterns did not appear to differ among the three strains. Both tumour type and location of tumours were also similar. No other types of cancer were found in the mice, indicating that osteosarcoma is the only specific plutonium-induced tumour in mice. These results are in broad agreement with those of a previously published study by the same authors, using the same mouse strains (Oghiso & Yamada, 2000), but differ from results obtained using CBA mice (Humphreys *et al.*, 1987).

(ii) Dog

Lloyd *et al.* (2001) updated the bone tumour incidence in dogs injected intravenously with ^{239}Pu Citrate published previously in Lloyd *et al.* (2000b), and showed a linear dose–response of osteosarcoma incidences versus average dose to the bone 1 year before death. ^{239}Pu was 16 times more effective than ^{226}Ra in producing bone tumours when compared, based on average skeletal dose. In an earlier paper, Taylor *et al.* (1991) also showed that injected ^{239}Pu caused liver cancer.

(c) Plutonium nitrate

Ellender *et al.* (2001) injected ^{239}Pu, ^{241}Am or ^{233}U intravenously into a different strain of mouse (CBA/H), and followed the animals for lifespan. There were clear dose–response-related incidences of osteosarcoma for the mice injected with either ^{239}Pu or ^{241}Am, with the former being about twice as carcinogenic per unit dose to bone; ^{233}U on the other hand showed little ability to increase bone cancer rates, and there was no dose–response relationship. For myeloid leukaemia, there was little, if any, difference in the increased incidence of the leukaemia for ^{239}Pu, ^{241}Am or ^{233}U, but the incidences were statistically significant, as determined using Cox hazard modelling. Significant increases in renal and hepatic carcinomas were also observed for the mice exposed to ^{233}U and ^{241}Am, respectively, but not for the other injection groups. The lack of consistent findings for the three radionuclides for tumours of the kidney and liver make the positive results uncertain, particularly in view of the significant incidence of disease in the control animals. Additionally, although the finding of a small but significant incidence of myeloid leukaemia in the CBA mouse has been repeatedly demonstrated with both radionuclides and external radiation, the results should be interpreted cautiously in view of the lack of observed leukaemia in other strains of mice that are known not to be sensitive to the induction of acute myeloid leukaemia (e.g. Oghiso & Yamada 2000, 2003b), and other species such as the dog (Lloyd *et al.*, 2001, 2004).

3.2.9 Curium-242 in insoluble form

(a) Mouse

Priest *et al.* (2006) exposed mice to either ^{45}Ca-FAP or ^{242}Cm-FAP [FAP; Fused Aluminosilicate Particles] aerosols by inhalation to study the relative ability of β-particles or α-particles in producing lung cancer when given in inhaled amounts that would result in relatively equivalent absorbed doses to the lung (i.e. a RBE study). There were four radiation dose groups ranging from about 0.5 Gy to about 5 Gy. Although there was an increased incidence of malignant lung tumours in the two highest dose groups for both radionuclides, only the ^{242}Cm in the lowest two groups had elevated cancer rates. It should be noted that the control lung cancer incidence was about 28% for these CBA/Ca mice. No other cancers of significance were noted, which was

expected given the relative insolubility of the aerosol carrier particles (FAP).

3.3 Other studies

Selby & Priest (2005) tested the hypothesis that male mice injected with ^{239}Pu Citrate would transmit mutations leading to somatic effects in their offspring by breeding ^{239}Pu-contaminated male CBA/Ca mice with uncontaminated females. Absorbed doses to the testes were calculated to be 0.3 and 4 Gy in the two experimental groups. After following the offspring for their lifespan, no evidence was found for leukaemia induction or any other probable causes of death. Interestingly, male progeny from both treated dose groups lived significantly longer than those from the controls.

Miller *et al.* (2003) compared the locations of osteosarcomas in ^{239}Pu-injected dogs with those described in studies of the Mayak workers who also had osteosarcomas. An almost identical distribution of ^{239}Pu-induced sarcomas was found for both populations, i.e. about 70% of the tumours were found in the axial skeleton. This distribution differs from that of naturally occurring sarcomas, in which about 60% of bone tumours occur in the peripheral or apendicular skeleton. These results support the model that plutonium retention and sarcomas have a preference for well vascularized, cancellous bone sites.

3.4 Synthesis

Several studies on the carcinogenic effects of α-particle-emitting radionuclides in experimental animals have appeared in the literature since the publication of the previous *IARC Monograph* (IARC, 2001). These include new data or data reanalysed from previous studies on ^{210}Po, ^{222}Rn, ^{226}Ra, ^{228}Th, ^{232}Th, ^{233}U, ^{237}Np, ^{239}Pu, ^{241}Am, and ^{242}Cm. Routes of exposure include intravenous or intraperitoneal injection, intramuscular implantation, intratracheal instillation, and inhalation, and species include mice (four strains), rats (two strains), Syrian hamsters, and beagle dogs. The data from these studies consistently support and confirm the conclusions that all of the studied α-particle-emitting radionuclides are clearly carcinogenic in experimental animals. Because the patterns of radiation dose for these α-particle emitters are typically non-uniform and specific to different tissues and organs, the site-specific cancer incidences vary based on the radionuclide, its physicochemical form, route of administration, and to a lesser degree, on the experimental animal.

It is likely that other α-particle-emitting radionuclides not included above also may be carcinogenic to the tissues and organs in which they are capable of depositing; however, lacking experimental evidence, it is not possible to indentify them explicitly.

4. Other Relevant Data

See Section 4 of the *Monograph* on X-radiation and γ-radiation in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of radon-222 and its decay products. Radon-222 and its decay products cause cancer of the lung. Also, a positive association has been observed between exposure to radon-222 and leukaemia.

There is *sufficient evidence* in humans for the carcinogenicity of underground haematite mining with exposure to radon. Underground haematite mining with exposure to radon causes cancer of the lung.

There is *sufficient evidence* in humans for the carcinogenicity of radium-224. Radium-224 causes bone sarcomas.

There is *sufficient evidence* in humans for the carcinogenicity of radium-226. Radium-226 causes bone sarcomas and carcinomas of the paranasal sinuses and mastoid process.

There is *sufficient evidence* in humans for the carcinogenicity of radium-228. Radium-228 causes bone sarcomas.

There is *sufficient evidence* in humans for the carcinogenicity of thorium-232 as stabilized thorium-232 dioxide in colloidal form (Thorotrast). Diagnostic injection of Thorotrast causes primary liver cancer, leukaemia (excluding chronic lymphocytic leukaemia), cancer of the extrahepatic bile ducts, and of the gallbladder. Also, positive associations have been observed between injection of Thorotrast and cancer of the pancreas and of the prostate.

There is *sufficient evidence* in humans for the carcinogenicity of plutonium-239. Plutonium-239 causes cancer of the lung, liver and bone.

There is *limited evidence* in humans for the carcinogenicity of mixtures of uranium isotopes.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ^{210}Po, ^{222}Rn, ^{224}Ra, ^{226}Ra, ^{228}Th, ^{230}Th, ^{232}Th, ^{233}U, $^{234, 235, 238}$U (natural, enriched and depleted uranium), ^{237}Np, ^{238}Pu, ^{239}Pu, ^{241}Am, ^{244}Cm, ^{249}Cf, ^{252}Cf.

The radionuclide ^{228}Ra may be considered a mixed β-particle emitter in two-year carcinogenicity bioassays with rodents (with truncation of the decay chain at ^{228}Th; half-life, 1.91 years), whereas the effects of α-particle radiation predominate in long-term human exposure.

Radon-222 with its decay products are *carcinogenic to humans (Group 1).*

Radium-224, radium-226, radium-228 are *carcinogenic to humans (Group 1).*

Thorium-232 (as Thorotrast) is *carcinogenic to humans (Group 1).*

Plutonium-239 is *carcinogenic to humans (Group 1).* The Working Group noted that human exposure to plutonium-239 may also include exposure to other plutonium isotopes.

Underground haematite mining with exposure to radon is *carcinogenic to humans (Group 1).*

Internalized radionuclides that emit α-particles are *carcinogenic to humans (Group 1).*

In making this overall evaluation, the Working Group took into consideration the following:

- α-Particles emitted by radionuclides, irrespective of their source, produce the same pattern of secondary ionizations, and the same pattern of localized damage to biological molecules, including DNA. These effects, observed *in vitro*, include DNA double-strand breaks, chromosomal aberrations, gene mutations, and cell transformation.
- All radionuclides that emit α-particles and that have been adequately studied, including radon-222 and its decay products, have been shown to cause cancer in humans and in experimental animals.
- α-Particles emitted by radionuclides, irrespective of their source, have been shown to cause chromosomal aberrations in circulating lymphocytes and gene mutations in humans *in vivo*.
- The evidence from studies in humans and experimental animals suggests that similar doses to the same tissues — for example lung cells or bone surfaces — from α-particles emitted during the decay of different radionuclides produce the same types of non-neoplastic effects and cancers.

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INTERNALIZED β-PARTICLE EMITTING RADIONUCLIDES

Internalized radionuclides that emit β-particles were considered by a previous IARC Working Group in 2000 (IARC, 2001). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

See Section 1 of the *Monograph* on X-radiation and γ-radiation in this volume.

2. Cancer in Humans

2.1 Pure β-particle emitters

2.1.1 Tritium

^{3}H is a radioactive isotope of hydrogen that emits low-energy β-particles. ^{3}H is readily taken into the body via inhalation, ingestion, and dermal absorption; once deposited in the body, ^{3}H acts as an internal emitter. While ubiquitous, the low magnitude of ^{3}H doses typical of environmental and occupational settings makes epidemiological research on the health effects of ^{3}H intakes difficult. Large studies are required to derive estimates with statistical stability, confounding must be minimized in order not to obscure or bias estimates of association that are often modest in low-dose settings, and exposure assessment must be of high quality to minimize bias due to measurement error. These requirements need to be given due consideration when evaluating the evidence on the carcinogenicity of β-particle irradiation arising from ^{3}H intakes.

The current review of the epidemiological literature focuses on studies of workers in the nuclear power and weapons industry for whom ^{3}H could have been an important contribution to the dose. While environmental releases of ^{3}H have led to large numbers of people exposed to low levels of ^{3}H, there have been few epidemiological studies of these exposures, and none has quantified doses from ^{3}H. This review gives primary attention to epidemiological analyses in which individuals' ^{3}H exposures were quantified permitting comparisons between groups with different exposure histories.

Several studies have considered the risk of prostate cancer and occupational exposures to radionuclides, including ^{3}H, among United Kingdom nuclear industry workers. Rooney *et al.* (1993) reported on a case–control study of UKAEA (United Kingdom Atomic Energy Authority) workers with follow-up through 1986, noting a significantly elevated relative risk of prostate cancer among workers with

documented intake of ^{3}H (RR, 14.26; 95%CI: 3.09–133.16). The excess was primarily associated with work in heavy-water reactors, and the risk of prostate cancer increased with increasing level of potential exposure to ^{3}H (*P* for trend < 0.05). Carpenter *et al.* (1998) examined cancer mortality in relation to monitoring for internal exposure to ^{3}H and other radionuclides among employees of three different cohorts: UKAEA, AWE (Atomic Weapons Establishment), and the Sellafield plant of British Nuclear Fuels Limited, all in the United Kingdom. Overall cancer mortality was significantly below national rates among workers monitored for ^{3}H exposure, but relative risks for prostate cancer increased with the number of years of exposure for those monitored for ^{3}H relative to those not monitored for any radionuclide: 1 year (RR, 0.31), 2–4 years (RR, 3.19), and 5+ years (RR, 2.26) of ^{3}H exposure. Atkinson *et al.* (2007) reported on a further analysis of prostate cancer among UKAEA workers including deaths up through 1997 (Atkinson *et al.*, 2007). ^{3}H doses were not quantified but information on ^{3}H-monitoring status was collected. Among workers monitored for ^{3}H, the initial finding for the increased risk of prostate cancer was confirmed (RR, 5.80; 95%CI: 2.15–15.66) but only a small excess was observed in the later period (RR, 1.20; 95%CI: 0.59–2.41).

Lung cancer incidence among 95430 males in the Canadian National Dose Registry was positively associated with radiation dose (Hazelton *et al.*, 2006). This study used a two-stage clonal expansion model to assess the effect of γ-radiation and tritium dose on lung cancer risk. [It was noted that although whole-body tritium exposures are generally small in comparison with gamma exposures, the dose–response for tritium considered separately was marginally significant.]

Several other cohort studies of nuclear industry workers have examined associations between radiation and cancer among nuclear industry workers incorporating ^{3}H dose estimates into whole-body dose estimates, but without conducting separate analyses examining the ^{3}H component of the whole-body dose (e.g. Wing *et al.*, 1991; Cragle & Watkins, 1998; McGeoghegan & Binks, 2001; Zablotska *et al.*, 2004; Cardis *et al.*, 2007; Richardson & Wing, 2007; Schubauer-Berigan *et al.*, 2007). Given the relatively small contribution of ^{3}H to whole-body dose in these cohorts, these studies provide little information about the risk specifically associated with ^{3}H intake.

The impact of releases to the environment on cancer rates have been the subject of investigations around various nuclear facilities, including several that released ^{3}H: the Savannah river site (Grosche *et al.*, 1999), the Krümmel facility (Grosche *et al.*, 1999), and several Canadian facilities (McLaughlin *et al.*, 1993). None of these studies included estimates of ^{3}H dose.

2.1.2 Phosphorus-32

^{32}P is a pure β-particle emitter with a physical half-life of 14.3 days. ^{32}P has been used as a therapeutic radiopharmaceutical for conditions including *polycythaemia vera* (Vinjamuri & Ray, 2008). Administered activities of ^{32}P are in the range of 1.85–2.96 × 10^{8} Bq, and estimates of the average skeletal dose of 300 rad per 7.4 × 10^{8} Bq [4 nGy/Bq] administered have been observed (IARC, 2001).

These doses far exceed the relatively low doses typical of occupational and environmental settings where people are internally exposed to other β-particle emitters, such as ^{3}H. While avoiding the problems associated with epidemiological studies of low doses, patients with radiotherapy treatment often also receive non-radiological treatments, which may confound interpretations of ^{32}P effects, and treated patients may differ from the general population in terms of the risk of developing a malignancy due to the underlying condition being treated (e.g. *polycythaemia vera*), or differ in susceptibility to the carcinogenic effects of irradiation.

A study by Modan & Lilienfeld (1965) provided strong evidence for the leukaemogenic effect of ^{32}P. Modan and Lilienfeld compared the occurrence of leukaemia among *polycythaemia vera* patients treated by phlebotomy, X-irradiation only, ^{32}P only, or a combination of X-irradiation and ^{32}P. The incidence of acute leukaemia was 11% in the 228 patients treated with ^{32}P but less than 1% in the 133 non-irradiated patients treated by phlebotomy only. Furthermore, the risk of leukaemia increased with increasing doses of administered ^{32}P.

Subsequent publications have confirmed the high risk of leukaemia in *polycythaemia vera* patients treated by ^{32}P (Najean *et al.*, 1996; Parmentier, 2003; Finazzi *et al.*, 2005). However, the interpretation of findings regarding ^{32}P leukaemogenicity in the contemporary literature comparing treatment protocols for patients with *polycythaemia vera* has been complicated by the fact that contemporary treatments other than ^{32}P also may be leukaemogenic (Parmentier, 2003).

Finazzi *et al.* (2005) reported on a study of 1638 patients with *polycythemia vera* enrolled in the European Collaboration on Low-dose Aspirin in Polycythemia Vera project (Finazzi *et al.*, 2005). A total of 21 cases of acute myeloid leukaemia and one case of myelodysplastic syndrome with rapid progression to acute myeloid leukaemia were diagnosed after a median of 2.5 years (range, 0.5–4.1 years) from the registration, and 8.4 years from the diagnosis of *polycythemia vera*. Patients undergoing phlebotomy or interferon therapy as the only cytoreductive agent could potentially represent the natural risk for *polycythemia vera* patients to progress to acute myeloid leukaemia, and were therefore treated as a reference category. The incidence rate of acute myeloid leukaemia/myelodysplastic syndrome (AML/MDS) was similar to those treated with phlebotomy or hydroxyurea at registration (approximately 0.29 per 100 persons per year), whereas this rate was 1.8 per 100 persons per year in those receiving at least one alkylating agent or ^{32}P at recruitment. Treatment by ^{32}P was significantly associated with risk of AML/MDS (hazard ratio (HR), 8.96; 95%CI: 2.13–37.58).

2.2 Mixed exposures

2.2.1 Caesium-137

Fallout from weapons testing in the 1950s and from the Chernobyl accident resulted in increased ^{137}Cs activity concentration in reindeer muscles, particularly during the winter season (Ahman & Ahman, 1994), which was fairly well correlated with caesium deposition in the reindeer pastures of Sweden (Ahman *et al.*, 2001). Lapps who breed reindeer in the northern parts of the Nordic countries and the Russian Federation have ingested fallout products via the lichen–reindeer–man food-chain since the 1950s.

A cohort of 2034 Lapps reindeer breeders and members of their households was followed in Sweden for cancer incidence and mortality during 1961–85 (Wiklund *et al.*, 1990, 1991). Both cancer mortality and incidence rates for all cancers combined were lower than in the Swedish population as a whole (SMR, 0.70; 95%CI: 0.56–0.87; SIR, 0.61; 95%CI: 0.05–0.75). This may reflect a healthier lifestyle and lower smoking prevalence compared to the general population. The stomach was the only site for which a significantly increased risk for cancer was found (SIR, 2.25; 95%CI: 1.46–3.32) when compared with national rates. [This finding was attributed to high intake of salt and other dietary habits.]

2.2.2 Fission products

Persons exposed as a result of releases from nuclear facilities can receive external doses from fission-product radionuclides deposited in the environment as well as internal doses from the

ingestion of foods containing fission products such as ^{137}Cs and ^{90}Sr (IARC, 2001).

^{137}Cs and ^{134}Cs, along with ^{131}I, were the main contributors to the internal dose populations exposed as a result of the Chernobyl accident. ^{137}Cs and ^{134}Cs were also the most important radionuclides for external doses for these populations (IARC, 2001).

Several ecological studies have examined possible associations between the risk of malignancies, especially childhood leukaemia, and average doses from external and internal exposures from the Chernobyl fallout, including the European Childhood Leukaemia–Lymphoma Study (ECLIS), the largest and most comprehensive study to date (Parkin *et al.*, 1992, 1996). The ECLIS study found no evidence of a radiation-related increase in the incidence of leukaemia in Europe in the first 5 years after the accident.

An ecological study conducted in Belarus and Ukraine (Pukkala *et al.*, 2006) found a significant 2-fold increase in risk of breast cancer during 1997–2001, in the most contaminated districts (average cumulative whole-body dose from internal and external exposure of 40.0 mSv or more) compared to the least contaminated districts (RR in Belarus, 2.24; 95%CI: 1.51–3.32; and in Ukraine, 1.78; 95%CI: 1.08–2.93). [The Working Group noted that the assessment of doses in these districts considered the possibility that a portion of the diet could be from outside of those districts.]

Almost 30000 people living along the Techa River were exposed to a complex mixture of radionuclides, largely ^{90}Sr and to lesser extent to ^{137}Cs, from the Mayak plutonium production and separation facility in the Russian Federation. Liquid radioactive waste was discharged into this river (Degteva *et al.*, 1996, 2002). Bone marrow and bone surfaces received high doses as a result of ^{90}Sr deposition, and the lower gastrointestinal tract was exposed as a result of the transit of unabsorbed radionuclides, mainly ^{90}Sr. Doses to other organs were primarily from a combination of external γ-ray exposures and internal γ-radiation from ingested ^{137}Cs (Kossenko *et al.*, 2005). Excess relative risks (ERRs)/Gy for deaths from all-solid cancer was 0.92 (95%CI: 0.2–1.7), and those for leukaemia, excluding chronic lymphocytic leukaemia, was 6.5 (95%CI: 1.8–24) (Krestinina *et al.*, 2005). Analyses of solid cancer incidence resulted in a similar estimate (ERR/Gy, 1.0; 95%CI: 0.3–1.9; Krestinina *et al.*, 2007). Nuclear weapons testing and production has resulted in large collective doses to the world's population, typically at low dose rates of radiation from internal exposure to a mixture of radionuclides.

Exposures to ^{90}Sr were particularly notable in the region around the Techa River, in the southern urals. During 1949–56, radioactive wastes were discharged directly into the river. People living along the river received internal exposures from the ingestion of radionuclides; ^{90}Sr was the main contributor to the internal exposure (Ostroumova *et al.*, 2006).

A long-term follow-up study of a cohort of residents was conducted, suggesting that risks of cancer mortality and incidence increased with increasing estimated committed dose in this population. Internal doses were reconstructed according to radionuclide intakes (also reconstructed), age-specific metabolism models, and models for dose distribution in the body. External doses were also received in this population; the external dose diminished more rapidly and consistently with distance than the internal dose. Consequently, the external component of the dose accounted for 49% of the total dose in the upper Techa, but only 6% in the lower Techa region. Considering leukaemia excluding chronic lymphocytic leukaemia, risk increased significantly with total (OR/Gy, 4.6; 95%CI: 1.7–12.3), internal (OR/Gy, 5.4; 95%CI: 1.1–27.2), and external red bone marrow (RMB) doses (OR/Gy, 7.2; 95%CI: 1.7–30.0). When the internal and external components of the total RBM dose were included simultaneously in the model, the magnitude of the external dose associated with

leukaemia (OR/Gy, 5.6; 95%CI: 1.3–24.2) was larger than the magnitude of the internal dose associated with leukaemia (OR/Gy, 3.5; 95%CI: 0.7–19.0; Ostroumova *et al.*, 2006).

The impact of ^{90}Sr releases to the environment on cancer rates have been the subject of several ecological investigations, characterizing both changes in exposure from fallout over time as well as ecological correlations between temporal patterns in ^{90}Sr levels and childhood cancer rates (Gould *et al.*, 2000; Mangano *et al.*, 2000).

2.3 Mixed β-particle emitters–radioiodines

Most of the information on the association between cancer risk and iodine isotopes comes from studies of the consequences of the Chernobyl accident. Studies of other populations exposed as a result of fallout or of medical exposures are generally less informative.

2.3.1 Chernobyl

(a) Cancer of the thyroid

Cancer of the thyroid accounts for approximately 3% of the total cancer incidence in more developed regions and 1% in less developed areas of the world general population (Jemal *et al.*, 2011). Although this is a relatively rare tumour, in the past several decades incidence rates have been increasing in most developed countries (Ferlay *et al.*, 2002). Descriptive epidemiological studies show marked international variation in the incidence of cancer of the thyroid, with the highest incidence reported in The Republic of Korea and New Caledonia (Ferlay *et al.*, 2010a, b). The substantial variations among world populations strongly suggest that environmental factors play a key role in the etiology of this cancer.

Cancer of the thyroid is of great concern in radiation protection, because large numbers of people have been exposed to radioiodines, which concentrate mainly in the thyroid, through environmental sources or for medical reasons. Exposure to radioiodines, particularly ^{131}I, comes from atmospheric nuclear weapons tests, accidental or routine emissions from nuclear power plants, and nuclear weapons production facilities (UNSCEAR, 2000a). In medical settings, radioactive iodine is the treatment of choice for thyrotoxicosis, and a common treatment for cancer of the thyroid (Gross *et al.*, 1999).

Until the Chernobyl accident, however, the carcinogenic effect of exposure to ^{131}I was considered to be small compared to that of external photon exposures (UNSCEAR, 1994), and this was attributed to differences in radiation quality and particularly exposure rates (Shore, 1992). In fact, little experience of the effects in children of iodine isotopes on the thyroid was then available, as most studies on the carcinogenic effects of ^{131}I had been conducted in adult populations: the number of young people exposed in these studies was, however, small (Holm *et al.*, 1988; Hamilton *et al.*, 1989; Robbins & Adams, 1989; Rallison *et al.*, 1990). In one cohort study of 35000 Swedish patients examined with ^{131}I, a small, non-significant increase in risk of developing thyroid cancer was observed among the 7% of the cohort that had been exposed before the age of 20 (SIR, 1.69; 95%CI: 0.35–4.93; Hall *et al.*, 1996).

After the Chernobyl accident, a wide range of thyroid doses was received by the inhabitants of the contaminated areas in the three affected countries. Doses varied with age at the time of the accident (being highest in those who were youngest at the time of the accident), level of ground contamination, rate and source of milk consumption. Reported individual thyroid doses ranged up to several tens of Gy, and average doses ranged from a few tens of mGy to several Gy (UNSCEAR, 2000b; Cardis *et al.*, 2006).

Other sources of exposure resulting from the Chernobyl accident also contributed to thyroid dose, including the intake of short-lived radioiodines (^{132}I, ^{133}I, and ^{135}I) and radiotelluriums

(^{131}Te and ^{132}Te), external irradiation from radionuclides deposited on the ground, and ingestion of ^{134}Cs and ^{137}Cs. For most individuals, however, these represented only a small percentage of the thyroid dose in comparison to exposure to ^{131}I (UNSCEAR, 2000b; United Nations Chernobyl Forum, 2006)

(i) Exposures in childhood

The main health effect of radiation from the accident observed to date is a dramatic increase in the incidence of thyroid cancer in persons exposed in childhood and adolescence (United Nations Chernobyl Forum, 2006). This increase was observed first in the early 1990s in Belarus, and continues until now in the most contaminated areas of Belarus, Ukraine, and the Russian Federation (Kazakov *et al.*, 1992; Stsjazhko *et al.*, 1995; UNSCEAR, 2000b; Jacob *et al.*, 2006). In the whole of Belarus, by 1995, the incidence of childhood thyroid cancer had increased to 4 cases per 100000 per year compared to 0.03–0.05 cases per 100000 per year before the accident. As time has progressed, the incidence rate of childhood thyroid cancers has returned to pre-accident levels, with the exception of an increase in incidence in adolescents. The overall number of thyroid cancer cases diagnosed in Belarus, Ukraine and in the four most contaminated regions of the Russian Federation during 1986–2002 among those who were children or adolescents at the time of the Chernobyl accident is close to 5000 (Cardis *et al.*, 2006; United Nations Chernobyl Forum, 2006).

Several epidemiological studies of thyroid cancer following exposure to radioactive iodines from the Chernobyl accident have been reported both in the most contaminated countries and in other European countries (UNSCEAR, 2000b), providing compelling evidence that the observed increase is related to iodine fallout from the Chernobyl accident. Results of case–control (Astakhova *et al.*, 1998; Cardis *et al.*, 2005; Kopecky *et al.*, 2006) and cohort (Tronko *et al.*, 2006) studies with individual thyroid dose estimation are shown in Table 2.1 (available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-05-Table2.1.pdf), together with those of the most recent ecological study (Jacob *et al.*, 2006). Estimates from the larger case–control studies in Belarus (Astakhova *et al.*, 1998; Cardis *et al.*, 2005) and the Russian Federation (Cardis *et al.*, 2005) and the cohort study in Ukraine (Tronko *et al.*, 2006) are similar though slightly lower than the estimate from studies of external radiation (Ron *et al.*, 1995). The ERR/Gy derived in the ecological study (Jacob *et al.*, 2006) is higher than those derived from the larger case–control and cohort studies, but lower than that from the case–control study in the Bryansk area (Kopecky *et al.*, 2006). The latter estimate is based on a small number of cases (n = 66), most with doses much lower than 1 Gy, and the confidence intervals are wide, overlapping those of the other case–control and cohort studies. Dose-related increases in the risk of follicular adenoma of the thyroid were also observed in the Ukrainian screened cohort (Zablotska *et al.*, 2008).

There is some indication that iodine deficiency at the time of exposure may increase the risk of developing thyroid cancer among persons exposed to ^{131}I as children (Shakhtarin *et al.*, 2003; Cardis *et al.*, 2005). Conversely, prolonged stable iodine supplementation in the years after exposure may reduce this risk (Cardis *et al.*, 2005). Further studies are needed to replicate these findings.

The relative contributions of ^{131}I, short-lived isotopes of iodine, external exposures and long-lived nuclides were considered in one case–control study (Cardis *et al.*, 2005), which concluded that the observed increased risk of thyroid cancer after the Chernobyl accident appears to be mainly due to ^{131}I. Doses from other radiation types were low, however, and it is difficult to evaluate the carcinogenic potential of shorter lived isotopes of iodine.

Papillary cancer is the primary pathological type of thyroid cancer found in those exposed as children and adolescents to fallout from the Chernobyl accident. It does not appear that the biology of radiation-induced thyroid cancer is fundamentally different from that seen in a non-irradiated population. A slightly greater percentage of radiation-induced thyroid cancers appear to be papillary in nature (Williams *et al.*, 2004). Possible differences in the molecular biology of the tumours, particularly with regard to proto-oncogene *RET/PTC* rearrangements and *BRAF* mutations, are unclear at this time (Detours *et al.*, 2005; Powell *et al.*, 2005).

(ii) Exposures in utero and preconception

Data on exposure to the embryonic/fetal thyroid are rare, raising questions about use of ^{131}I in pregnant women. A total of seven cases of thyroid carcinoma were identified during 2003–06 in a cross-sectional thyroid screening study of children who were *in utero* at the time of the accident and whose mothers were part of a cohort with direct thyroid measurements in Ukraine. Of these, six cases were diagnosed among the 1494 children from contaminated areas, and one from the comparison group of 1088 children from less contaminated areas. Individual cumulative in-utero thyroid dose estimates were derived from estimated ^{131}I activity in the mothers' thyroid (mean 72 mGy; range 0–3230 mGy). The estimated excess odds ratio per grey for thyroid cancer was 11.66 (95%CI: < 0–1982; Hatch *et al.*, 2009).

Effects of in-utero and preconception exposure were also investigated in a cross-sectional screening survey of children from the Gomel region of Belarus living in five areas that were within 150 km of the Chernobyl nuclear power plant (Shibata *et al.*, 2001). One case of thyroid cancer was identified among 2409 children who were *in utero* at the time of the accident compared to 31 among 9720 children exposed in the first three years of their life. No cases were diagnosed among the 9472 children screened who were conceived in the three years following the accident.

(iii) Exposures in adults

Although the increased risk of thyroid cancer in those exposed in childhood and adolescence is well demonstrated, the effect of exposure on adults remains unclear. Increased incidence of thyroid cancer was reported among 60000 liquidators, 50000 evacuees, and 360000 residents of the most contaminated areas of Ukraine (Prysyazhnyuk *et al.*, 2007); among the latter, the increase appeared to be related to radioiodine fallout. An increased incidence of thyroid cancer was also reported in cohorts of liquidators from Belarus and the Russian Federation (Okeanov *et al.*, 1996; Ivanov *et al.*, 1997) compared to the general population of these countries and, more recently, based on small numbers of cases in a Baltic cohort of liquidators from Estonia and Latvia (Rahu *et al.*, 2006). [The Working Group noted that the possible effect of differential screening among liquidators and in regions with different levels of contamination (Cardis & Okeanov, 1996; UNSCEAR, 2000b) could, however, at least partially explain these observations.] Among residents of contaminated areas of the Russian Federation, no dose–response relationship was found for thyroid cancer following exposures in adulthood (Ivanov *et al.*, 2003).

(b) Other cancers

The highest organ-specific radiation doses from the Chernobyl accident were to the thyroid gland; exposure occurred primarily from ingestion of milk contaminated with radioactive iodines, particularly ^{131}I, and epidemiological studies of the effects of radioiodines after Chernobyl have therefore focused on the risk of thyroid diseases. No analytical study of other endpoints in relation to radioiodines was therefore available for review.

2.3.2 Other environmental exposure to radioiodines

(a) Cancer of the thyroid

Table 2.2 (available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-05-Table2.2.pdf) summarizes studies of thyroid cancer risk following exposure to radioiodines from fallout from atmospheric weapons testing, and from releases from the Hanford plant in Washington State in the USA.

In the Marshall Islands study (Takahashi *et al.*, 1999, 2001), two surrogate measures of radiation dose were derived for the subjects who were alive at the time of the BRAVO test. Associations were found between the risk of thyroid cancer and both of these measures. No association was found between estimated thyroid dose and risk of thyroid cancer in the Hanford study (Davis *et al.*, 2004). A statistically significant association was found between estimated radioiodine dose from the Nevada test site and risk of thyroid neoplasms in Utah, Nevada, and Arizona, (Lyon *et al.*, 2006), based on revised thyroid dose estimates and a detailed assessment of dosimetric uncertainties. Numbers of cases in each of the studies were small, however, compared to those in the aforementioned Chernobyl studies.

(b) Other cancers

As in the case of Chernobyl, the highest organ-specific radiation doses from the releases were to the thyroid gland. No analytical study of other end-points in relation to radioiodines was therefore available for review.

2.3.3 Medical exposures to ^{131}I

^{131}I is currently the treatment of choice for hyperthyroidism and thyroid cancer, and is used broadly for diagnostic investigations of thyroid diseases.

(a) Cancer of the thyroid

As indicated in Volume 78 of the *IARC Monographs* (IARC, 2001), several studies of the carcinogenic effect of radioiodine involved patients treated for hyperthyroidism (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-05-Table2.3.pdf). Significantly increased risks of thyroid cancer were seen overall in some studies of patients treated for hyperthyroidism, based on small numbers of cases (Hall *et al.*, 1992; Ron *et al.*, 1998; Franklyn *et al.*, 1999). No study focused specifically on populations exposed to ^{131}I in childhood or adolescence for the treatment of hyperthyroidism; furthermore, there were very small numbers of subjects below the age of 20 years at diagnosis in the hyperthyroidism cohorts. In a review paper, however, Shore (1992) carried out an analysis of risk in those exposed below the age of 20 years in the Swedish and US studies. The total population was estimated to be 602 with an approximate average follow-up of 10 years and a mean dose to the thyroid of about 88 Gy. A total of two cases of thyroid cancer were reported, compared to about 0.1 expected. The estimated ERR/Gy was 0.3 (90%CI: 0.0–0.9) and the EAR was 0.1×10^{-4} PY/Gy (90%CI: 0.0–0.2).

The risk of thyroid cancer following diagnostic examination with ^{131}I was studied in a cohort of about 35000 patients below the age of 75 years (Holm, 1991). In a further follow-up of this cohort up to 1998, excess thyroid cancer risk was seen only for those who received previous external radiation therapy to the neck and those who were referred due to suspicion of thyroid tumours (Dickman *et al.*, 2003).

(b) Other cancers

The risk of any cancer following diagnostic examination with ^{131}I was also studied in a Swedish cohort of about 35000 patients below the age of 75 years (Holm, 1991). An increased risk of second cancers was observed 5–9 years after

examination (SIR, 1.07; 95%CI: 1.01–1.14, based on 964 cases).

Increases in the risk of tumours at other sites have been reported in populations of patients treated with ^{131}I for benign or malignant thyroid conditions.

In a US study, the incidence of leukaemia following treatment of hyperthyroidism did not differ between a group of 22000 patients treated with ^{131}I and those treated surgically (Saenger *et al.*, 1968), nor was it increased in a study of 10552 patients treated in Sweden during 1950–75 (Holm *et al.*, 1991) or in a study of 2793 patients treated during 1965–2002 in Finland (Metso *et al.*, 2007).

In the same study in Sweden, the SIR for all cancers was 1.06 (95%CI: 1.01–1.11) compared to the Swedish population (Holm *et al.*, 1991); it was 1.25 (95%CI: 1.08–1.46) in the Finnish study (Metso *et al.*, 2007).

In the Swedish study, significant increases were seen for cancers of the lung and kidney and, among 10-year survivors, for cancers of the stomach, kidney and brain. Only the risk for stomach cancer, however, increased with the level of administered ^{131}I dose, and this increase was not statistically significant; the estimated relative risk at 1 Gy for stomach cancer was 2.32, and the absolute risk was 9.6×10^{-4} PY/Gy (Holm *et al.*, 1991).

In the Finnish study, the incidence of stomach, kidney and breast cancer was increased among patients treated with radioiodines, and the relative risk increased with the level of radioiodines administered (Metso *et al.*, 2007).

In patients treated for thyroid cancer, no significantly increased risk of leukaemia or breast cancer was observed in a study of 834 patients from Sweden (Hall *et al.*, 1991), though increased incidences were observed for tumours of the salivary gland, genital organs, kidney and adrenal gland in women. These increases could not, however, be linked to high-dose ^{131}I exposures.

In combined analyses of data on 4225 thyroid cancer cases treated with ^{131}I in France, Italy and Sweden (Rubino *et al.*, 2003), increased risks of solid tumours, leukaemia, colorectal cancer and soft tissue and bone sarcoma were observed with increasing cumulative activity of ^{131}I administered. A significant association was also found between ^{131}I administration and the occurrence of bone and soft tissue, female genital organs, and salivary gland cancers, but not breast cancer. A marginally significant association was seen for tumours of the central nervous system (RR, 2.2; 95%CI: 0.9–5.7). For colorectal cancer, a role for cancer susceptibility in the carcinogenic response to radioiodine was suggested in a study that used familial aggregation as a proxy of inherited cancer susceptibility in a nested case–control study within the French cohort of thyroid cancer patients (Rubino *et al.*, 2005).

In a study of 875 patients from France, an overall increased risk of second primary malignancies was seen in women but not in men (Berthe *et al.*, 2004); the increased risk was related to cancer of the genitourinary tract and cancer of the kidney. Cumulative activity of ^{131}I was not, however, related to the risk.

In a study of 30278 thyroid cancer patients in the US, a significantly increased risk of second primary malignancies (in particular all cancers, leukaemia, stomach and prostate cancer) was seen for patients treated with radioisotopes (Brown *et al.*, 2008). Non-significant increases were seen for breast cancer and cancers of the central nervous system. The greatest risk of second malignancies was seen within 5 years of diagnosis, however, and no information about level of ^{131}I activity was available.

2.4 Synthesis

Relatively few epidemiological studies have assessed the carcinogenic effects of ^{3}H intakes in human populations; the typically low doses encountered in occupational and environmental

settings pose challenges for epidemiological studies of this radionuclide. The most detailed investigation of this question has involved UKAEA workers. These studies noted a significantly elevated relative risk of prostate cancer among workers with documented intake of ^{3}H that tended to increase in magnitude with duration of ^{3}H monitoring; this association diminished in magnitude in more recent calendar years of follow-up; however, ^{3}H doses were not quantified and there is potential for confounding by other occupational exposures.

The epidemiological literature provides consistent evidence of an elevated risk of leukaemia among patients treated with ^{32}P, and the study by Modan & Lilienfeld (1965) showed a significant association between ^{32}P treatment and the occurrence of acute leukaemia in *polycythaemia vera* patients. Modan & Lilienfeld (1965) also demonstrated a dose–response association between ^{32}P and leukaemia. Subsequent studies, although methodologically weaker for drawing inferences on specific effects of ^{32}P, support the observation of elevated rates of acute leukaemia among patients treated by ^{32}P relative to patients treated by phlebotomy (Parmentier, 2003; Finazzi *et al.*, 2005).

No new study was available to the working group that allows the evaluation of the possible carcinogenic effect of ^{137}Cs on its own. For studies of mixed exposures, see Section 2.1.4.

Based on the increased risk of solid cancers and of leukaemia among residents of the Techa River area, the working group considered that the mixture of external exposure and internal exposures predominantly to ^{90}Sr causes cancer in humans.

Since the previous *IARC Monograph*, the evidence relating risk of thyroid cancer and exposure to radioiodines in childhood and adolescents from the Chernobyl accident has increased substantially, with several carefully conducted analytical epidemiological studies with individual dose estimation. Increased risks are also suggested for exposure to radioiodines from fallout from the Nevada and Marshall Islands atmospheric weapons tests. Information from studies of radioiodines from fallout about effects on thyroid cancer of exposure in adults remains scarce. The effect of exposures to radioiodines from fallout on the risk of tumours other than the thyroid has not been studied adequately.

Information from studies of medically exposed cohorts has increased since the previous *IARC Monograph* (IARC, 2001). More recent studies of cohorts of patients treated with ^{131}I indicate an increased risk of cancer. Increases in the risk of cancers at a variety of sites, including breast, central nervous system, kidney, digestive tract, salivary gland, as well as bone and soft tissue sarcoma and leukaemia have been reported in several studies. These observations may be related to detection and/or surveillance bias, shared genetic or environmental risk factors, or, in the case of cancer survivors, to ^{131}I treatment.

To date, most studies lack detailed information on levels of administered ^{131}I. In the studies that did evaluate this, however, apparent activity-related increases were observed for tumours of the salivary gland and digestive tract, for leukaemia and for bone and soft tissue sarcoma, but not for breast cancer.

3. Cancer in Experimental Animals

3.1 Previous evaluation

All radionuclides that emit β-particles that have been adequately studied, have been shown to cause cancer in experimental animals.

Lifetime studies of the carcinogenic effects of pure and mixed β-particle-emitting radionuclides have been conducted in experimental animals of several species that differ greatly in features such as size, metabolic characteristics, and lifespan. The locations and types of tumours observed were influenced by several factors

including the form of the radionuclide, the route by which it was administered, the resulting metabolic and dosimetric patterns, the age, sex and health status of the animals, and the presence of other agents.

Because the penetration of β-particles is usually greater than that of α-particles, effects on tissues may be seen not only at the primary site of radionuclide deposition, like the skeleton, but also in nearby tissues like the nasal or oral mucosa.

Since the previous *IARC Monograph* (IARC, 2001), only one study has been been published on the carcinogenicity of β-particle-emitting radionuclides in experimental animals. Thus, the Working Group reviewed the studies in the previous *IARC Monograph* and incorporated the experimental animals studies on other β-particle-emitting radionuclides that were not considered in the previous *IARC Monograph*.

3.2 Pure β-particle-emitting radionuclides

3.2.1 Tritium

The carcinogenicity of ^{3}H administrated as tritiated water ($^{3}H_2O$) was tested in mice by intraperitoneal injection (Johnson *et al.*, 1995) or oral administration (Yamamoto *et al.*, 1998), and in rats by intraperitoneal injection (Gragtmans *et al.*, 1984) producing thymic lymphoma and myeloid leukeamia in mice and mammary tumours [tumour type not specified] in rats.

3.2.2 Phosphorus-32

^{32}P injected intraperitoneally as Na_3PO4 to mice increased the incidence of leukaemia (Holmberg *et al.*, 1964). In rats, intraperitoneal injection of ^{32}P in an unspecified form produced osteogenic sarcomas (Koletsky *et al.*, 1950).

3.2.3 Strontium-90

^{90}Sr produced bone and lymphoid tumours in mice after its intraperitoneal injection as $^{90}Sr(NO_3)_2$ (Nilsson *et al.*, 1980). It produced osteosarcomas in dogs after intravenous injection, haemangiosarcomas were also found in dogs following inhalation and ingestion at a soluble form (Gillett *et al.*, 1992) and miniature pigs fed strontium-90 in the diet (NCRP, 1991).

3.2.4 Yttrium-90 and Yttrium-91

^{90}Y inhaled in an insoluble form produced lung cancers in dogs (Boecker *et al.*, 1994). ^{91}Y produced carcinomas and adenocarcinomas, lung, liver carcinomas and bone-associated nasal and oral mucosa tumours (squamous cell carcinomas and malignant melanoma) in dogs that inhaled a soluble form $^{91}YCl_3$ (Muggenburg *et al.*, 1998), and lung cancers in dogs that inhaled an insoluble form of $^{91}YCl_3$ (Boecker *et al.*, 1994).

3.2.5 Promethium-147

^{147}Pm caused lung adenomas, adenocarcinomas and epidermoid carcinomas tumours in Syrian hamsters injected intravenously with insoluble particles (Anderson *et al.*, 1979), and lung haemangiosarcomas and squamous cell carcinomas in rats exposed by inhalation (Herbert *et al.*, 1987, 1988).

3.2.6 Lutetium-177 and Samarium-153

Müller *et al.* (1980) studied the lifespan biological effects of two short-lived β-emitting radionuclides, ^{177}Lu (6.7 days half-life) and ^{153}Sm (47 hours half-life), injected intraperitoneally into weanling groups of 50 female NMRI mice 4 weeks of age. Both of these radionuclides are used in diagnostic and therapeutic nuclear medicine. Statistically significant incidences 6/48 (12.5%), 18/51 (35.5), 18/48 (37.5%) of osteosarcomas were noted in the mice injected with ^{177}Lu at injected

doses of 185 MBq/kg, 370 MBq/kg and 740 MBq/kg, respectively, compared to 0/50 animals in the control group. Animals injected with the highest dose (1480 MBq/kg) suffered severe damage to their incisors, a phenomenon that was also noted with ^{32}P (Bauer *et al.*, 1957). Consequently, these animals could not eat and were killed before they could develop bone cancer. Osteosarcomas from the short-lived ^{177}Lu occurred in the same dose range as those observed for the long-lived bone-seeking radionuclide, ^{90}Sr, i.e. 20–80 Gy. The lifespan study with intraperitoneally injected ^{153}Sm did not produce any osteosarcomas. This was evidently due to the use of a significant quantity of stable Sm carrier in the injection solution. Based on an observed significant shift of deposition of ^{153}Sm from bone to liver, compared to that for ^{177}Lu, it was concluded that the addition of 2 mg/kg Sm carrier resulted in the creation of colloidal species, which were taken up preferentially in organs rich in reticuloendothelial elements like the liver and spleen. As a result, severe degenerative changes in the liver were produced, but without liver cancer (Müller *et al.*, 1980).

3.3 Mixed β-particle emitting radionuclides

3.3.1 Calcium-45

Priest *et al.* (2006) exposed four groups of 160 female CBA/Ca mice by inhalation (nose-only) at four dose levels (0.5 Gy to about 5 Gy) to β particles from ^{45}Ca-labelled fused aluminosilicate particles (AFP) or to carrier AFP (400 mice). This was to study the relative ability of β particles in inducing lung cancer when given in inhaled amounts that would result in relatively equivalent absorbed doses to the lung, in producing lung cancer (i.e. RBE study). The target initial alveolar deposits (IADs) for the radionuclide were 0.8, 4.8, 8.8 and 12.8 kBq. Another group of 120 mice inhaled no AFP and were designated as untreated controls. The incidence of mice with malignant lung tumours after inhalation of carrier control AFP was 105/371 (28.3%). This incidence was not significantly different from the incidence of untreated mice with spontaneous lung tumours 36/124 (29%). A consistently higher number of mice with malignant lung tumours was observed in all of the ^{45}Ca-AFP-exposed groups (38/114, 33.3%; 33/109, 30.0%; 44/112, 39.3%; 53/109, 48.6%) compared with the carrier control and untreated control groups. This difference reached significance ($P < 0.05$ to $P < 0.001$) for all groups except for those that received the two lowest ^{45}Ca-AFP doses.

3.3.2 Iodine-131

^{131}I given by intraperitoneal injection to mice and rats produced thyroid adenocarcinomas, alveolar, follicular, and papillary carcinomas (Lindsay *et al.*, 1957; Walinder, 1972; Lee *et al.*, 1982).

3.3.3 Caesium-137

^{137}Cs produced malignant neoplasms (neurofibrosarcomas, haemangiosarcomas, carcinomas and cholangiocarcinomas) in the liver, biliary system, endocrine system (thyroid adrenal and pituitary glands), urinary system haemangiosarcomas and neoplasms in the renal haematopoietic system, genital system, and the respiratory system after intravenous injection to dogs (Nikula *et al.*, 1995, 1996).

3.3.4 Cerium-144

^{144}Ce inhaled in an insoluble form ($^{144}CeO_2$) produced lung adenomas, adenocarcinomas and squamous cell carcinomas in mice, rats, Syrian hamsters and dogs (Lundgren *et al.*, 1980 a, b, 1982, 1992a, b, 1996; Hahn & Lundgren, 1992), and lymph nodes and heart haemangiosarcomas in dogs (Hahn *et al.*, 1999). Dogs that inhaled a soluble form of ^{144}Ce ($^{144}CeCl_3$) developed lung,

liver, bone, oral and nasal mucosal, and haematopoietic neoplasms (Hahn *et al.*, 1995, 1997).

3.3.5 Radium-228

^{228}Ra may be considered a mixed β-particle emitter in 2-year carcinogenicity bioassays. ^{228}Ra produced osteosarcomas in dogs after intravenous injection (Mays *et al.*, 1987; Lloyd *et al.*, 1997).

3.4 Synthesis

A small number of studies on the carcinogenic effects of β-emitting radionuclides in experimental animals have been analysed or reanalysed since the previous *IARC Monograph* (IARC, 2001). These include results from studies on exposure to ^{45}Ca, ^{153}Sm, ^{177}Lu by intravenous injection and inhalation in mice and rats. The data from these studies support and confirm the Working Group's conclusions that all of the studied β-emitting radionuclides are carcinogenic (IARC, 2001). Because the patterns of radiation dose for these β-emitters are often non-uniform and specific to different tissues and organs, the site-specific cancer incidences vary based on the radionuclide, its physicochemical form, and route of administration.

4. Other Relevant Data

See Section 4 of the *Monograph* on X-radiation and γ-radiation in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of exposure during childhood and adolescence to short-lived radioisotopes of iodine, including iodine-131. Exposure during childhood and adolescence to short-lived radioisotopes of iodine, including iodine-131, causes cancer of the thyroid. Also, positive associations have been observed between exposure to iodine-131 and cancer of the digestive tract and salivary gland, leukaemia, and bone and soft tissue sarcoma.

There is *sufficient evidence* in humans for the carcinogenicity of therapeutic administration of phosphorus-32, as phosphate. Therapeutic administration of phosphorus-32, as phosphate, causes acute leukaemia in patients with *polycythaemia vera*.

There is *sufficient evidence* in humans for the carcinogenicity of external exposure and internal exposure to fission products, including strontium-90. External exposure and internal exposure to fission products, including strontium-90, causes solid cancers and leukaemia.

There is *limited evidence* in humans for the carcinogenicity of strontium-90. A positive association has been observed between exposure to strontium-90 and leukaemia.

There is *inadequate evidence* in humans for the carcinogenicity of hydrogen-3.

There is *inadequate evidence* in humans for the carcinogenicity of caesium-137 alone or in combination with external radiation.

There is *sufficient evidence* in experimental animals for the carcinogenicity of the following β-emitting radionuclides: ^{3}H, ^{32}P, ^{90}Sr, ^{90}Y, ^{91}Y, ^{131}I, ^{137}Cs, ^{144}Ce, ^{147}Pm, ^{228}Ra.

There is *limited evidence* in experimental animals for the carcinogenicity of calcium-45 and Lutetium-177.

The radionuclide ^{228}Ra may be considered a mixed β-emitter in two-year carcinogenicity bioassays with rodents (with truncation of the decay chain at ^{228}Th; half-life, 1.91 years), whereas the effects of α-radiation predominate in long-term human exposure.

Short-lived radioisotopes of iodine, including Iodine-131 (^{131}I), are *carcinogenic to humans (Group 1).*

Phorphorus-32 (^{32}P), as phosphate, is *carcinogenic to humans (Group 1)*.

Mixtures of fission products are *carcinogenic to humans (Group 1)*.

Internalized radionuclides that emit β particles are *carcinogenic to humans (Group 1)*.

In making this overall evaluation, the Working Group took into consideration the following:

- β-Particles emitted by radionuclides, irrespective of their source, produce similar patterns of secondary ionizations and the same type of localized damage to biological molecules, including to DNA. These effects include DNA double strand breaks, chromosomal aberrations, gene mutations and cell transformation.
- All radionuclides that emit β-particles and that have been adequately studied, have been shown to cause cancer in humans and in experimental animals. This includes hydrogen-3, which produces β-particles of very low energy, but for which there is nonetheless *sufficient evidence* of carcinogenicity in experimental animals.
- β-Particles emitted by radionuclides, irrespective of their source, have been shown to cause chromosomal aberrations in circulating lymphocytes and gene mutations in humans in vivo.
- The evidence from studies in humans and experimental animals suggests that similar doses to the same tissues — for example lung cells or bone surfaces — from β -particles emitted during the decay of different radionuclides produce the same types of non-neoplastic effects and cancers.

All types of ionizing radiation are *carcinogenic to humans (Group 1)*.

In making this overall evaluation, the WG considered:

- All types of ionising radiation, even the neutron particle, transfer their energy to biological material as either divided or in clusters of ionization and excitation events, primarily through a free-electron-mediated mechanism.
- In cells, energy deposition from all types of ionizing radiation results in a wide variety of molecular damage; in DNA this includes base damage and single- and double-strand breaks, some of which may be clustered and form complex lesions. Subsequent processing of these lesions may lead to chromosomal aberrations and mutations.
- Much evidence points to damage to DNA being of primary importance in the biological outcome of exposure to ionising radiation.

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LIST OF ABBREVIATIONS

$^{1}O_{2}$	singlet oxygen
$^{2}H_{2}O$	heavy water
$^{3}H_{2}O$	tritiated water
A-bomb	atomic bomb
ADME	absorption, distribution, metabolism and excretion
AFP	fused aluminosilicate particles
AML	acute myeloid leukaemia
APE1	apurinic/apyrimidinic endonuclease-1
APRT	adenine phosphoribosyltransferase
ATM	Ataxia-telangiectasia
AVHRR	Advanced Very High Resolution Radiometer
AWE	Atomic Weapons Establishment
bFGF	basic fibroblast growth factor
CANDU	CANada Deuterium Uranium
CFCs	chlorofluorocarbons
CHO	Chinese hamster ovary
CIE	Commission Internationale de l'Eclairage
CNS	central nervous system
CO2	carbon dioxide
COX-2	cyclooxygenase-2
CpG	5′CG-3′ dinucleotide
CSA	cockayne syndrome A
CT	computed tomography
DMBA	7,12-dimethylbenz[a]anthracene
DS02	Dosimetry System 2002
EAR	excess absolute risk
ECLIS	European Childhood Leukaemia–Lymphoma Study
EPHA2	ephrin receptor A2
ERCC1	excision repair cross-complementing rodent deficiency, complementation group 1
ERR	excess relative risk
eV	electron-volt
FAP	Fused Aluminosilicate Particles
GG	global genome
GGR	global genome repair
GWAS	genome-wide association studies
$H_{2}O_{2}$	hydrogen peroxide
HCFCs	hydrochlorofluorocarbons

HGF/SF	hepatocyte growth factor/scatter factor
HIV	human immunodeficiency virus
hOGG1	human 8-oxoguanine DNA glycosylase
HPRT	hypoxanthine-guanine phosphoribosyltransferase
HPV	human papilloma virus
HR	hazard ratio
HSV	herpes simplex virus
IADs	initial alveolar deposits
IL-6R	interleukin-6 receptor
INK4a	inhibitor of cycline-dependant kinase 4 & 6
IRF4	interferon regulatory factor 4
IRSCCP	International Radiation Study of Cervical Cancer Patients
keV	kilo eV
LET	linear energy transfer
LSS	Life Span Study
MAPKs	Mitogen-activated protein kinases
MATP	membrane-associated transporter protein
MC1R	melanocortin-1 receptor
MDS	myelodysplastic syndrome
MED	minimal erythemal dose
MeV	mega eV
MM	malignant melanoma
NADPH	nicotinamide adenine dinucleotide phosphate
NER	nucleotide excision repair
NOS	not otherwise specified
NRRW	National Registry for Radiation Workers
O_2^-	superoxide anion radical
OCA2	blue eye oculocutaneous albinism type II
OMI	Ozone Monitoring Instrument
OR	odds ratio
PET	positron emission tomography
PKCε	protein kinase C epsilon
PO_4^{2-}.	phosphate
PTCH	patched gene
PTEN	phosphatase and tensin homologue gene
PUVA	psoralen with UVA radiation
PY	person-years
py–py	pyrimidine–pyrimidine
RAG-1	recombinase activating gene-1
RANKL	receptor activator of NF-κB ligand
RBE	relative biological effect
REF-1	redox factor-1
RMB	red bone marrow
RMBK	Russian reactor Bolshoy Moschnosti Kanalniy
RR	relative risk
RTK	receptor tyrosine kinase
SaDa	Solar Data Base
SCC	squamous cell carcinomas
SCF	steam cell factor
SCT	spindle cell tumour

SED	Standard Erythema Dose
SHH	sonic hedgehog homologue signaling pathway
shRNA	short-hairpin RNA
SIR	standardized incidence ratio
SMOH	smoothened gene
SMR	standardized mortality ratio
SNPs	single nucleotide polymorphisms
SPECT	single photon emission computed tomography
Sv	sievert
TC	transcription-coupled
Th1	T helper1
ThO2	Thorium dioxide
TNF	tumour necrosis factor
TOMS	Total Ozone Mapping Spectrometer
TPA	12-*O*-tetradecanoylphorbol-13-acetate
TYR	tyrosinase
UCA	urocanic acid
UKAEA	United Kingdom Atomic Energy Authority
UO_2^{2+}	uranyl ion
UV	Ultraviolet
UV-DDB	UV damaged DNA-binding
UVR	Ultraviolet radiation
WL	working-level
WLM/yr	working-level month/year
XAB2	XPA-binding protein-2
XPA	Xeroderma pigmentosum group A
XPF	Xeroderma pigmentosum group F
ZIP	Zoning Improvement Plan

CUMULATIVE CROSS INDEX TO *IARC MONOGRAPHS*

The volume, page and year of publication are given. References to corrigenda are given in parentheses.

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

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