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Methods for estimating the probability of cancer from occupational radiation exposure

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METHODS FOR ESTIMATING THE PROBABILITY OF CANCER FROM OCCUPATIONAL RADIATION EXPOSURE

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To the Reader,

This IAEA-TECDOC has been prepared for information and assistance in establishment and use of national registries for actinide elements in humans. Any proposals or comments that might help in updating this report would be most welcome.

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FOREWORD

The IAEA is aware that a few Member States, with well developed nuclear programmes, have initiated and developed schemes to compensate those workers (or their relatives) in whom cancer may have arisen from the exposure to radiation at work. Most of the Member States have however not yet developed similar schemes.

A Technical Committee meeting was held in July 1995 to provide information regarding experience on and techniques for making quantitative estimates concerning the probability of causation of cancer as a function of occupational radiation exposure and the methods of calculating and estimating whether occupational exposure of an individual suffering from cancer could be held responsible for the patient's condition.

In the case of a particular cancer in a specific individual it is generally accepted in existing schemes that compensation of a claimant who has worked with sources of ionizing radiation is appropriate if the probability of induction of this cancer from occupational radiation exposure is greater than the chance of induction by all other causes, including natural and medical radiation exposure. This publication discusses methods for assessing the probability of causation of cancer from occupational exposure taking into account a number of complex factors such as cumulative dose and duration of occupational exposure, dose rate, age at time of diagnosis of cancer, localization and type of cancer induced.

The participation of all members of the Technical Committee meeting in drafting the report is appreciated. The major contribution of J.R. Harrison (NRPB, UK) in the preparation of this report is especially acknowledged.

The Scientific Secretary responsible for the co-ordination of the meeting and the preparation of this publication was I. Turai of the Division of Radiation and Waste Safety.

EDITORIAL NOTE

In preparing this publication for press, staff of the IAEA have made up the pages from the original manuscript(s). The views expressed do not necessarily reflect those of the governments of the nominating Member States or of the nominating organizations.

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CONTENTS

1. INTRODUCTION

1.1. BACKGROUND

With increasing public awareness of the presumed risk of harm to health attributable to use of nuclear energy, there is an increasing number of claims for compensation by workers (or their relatives) in whom cancer may have arisen from the exposure to radiation at work.

A Technical Committee was formed to examine whether an IAEA Technical Document could provide guidance to Member States on the methods to be employed to calculate the probability that any particular cancer might be attributed to an occupational exposure to radiation.

1.2. OBJECTIVE

The aims of this TECDOC are to present the factors which are generally accepted as being responsible for cancer induction, to examine the role of radiation as a carcinogen, to demonstrate how the probability of cancer causation by radiation may be calculated and to inform the reader of the uncertainties that are associated with the use of various risk factors and models in such calculations.

1.3. SCOPE

This report considers only cancer induction and does not include other stochastic effects, such as hereditary disorders, or deterministic effects, such as cataract formation. It relates only to occupational radiation exposures. It does not include medical exposures, exposures ***in utero***, to embryos or fetuses of female radiation workers, doses from high natural background radiation, doses received from environmental exposures caused by industrial processes, or exposures to non-ionizing radiation.

1.4. APPLICATION, STRUCTURE

This report is intended for general guidance only. It outlines an approach to develop national procedures for calculating attributability when cancer cases arise in radiation workers who may be seeking compensation. It is not intended to be an authoritative reference on the subject but an aid to Member States for consideration of probability of occupational cancer induction. In any specific application the most up to date and appropriate risk factors and, where appropriate, national cancer incidence rates should be used.

Sections 2 and 3 give a brief review on aetiology of cancer in general and on its radiation origin, respectively. Section 4 introduces a basis for the choice of the appropriate risk model. In Section 5 the definition, limitations and the expression of the probability of causation for multiple exposure are presented. Section 6 outlines sources of uncertainty associated with epidemiological and dosimetric data, extrapolations, radiosensitivity, contribution of other carcinogenes or types of radiation.

Section 7 of this report includes some theoretical calculations (in 15 examples) and highlights the important parameters which are necessary to enable such calculations to be employed correctly. Factors affecting cancer risk are presented in Appendix I, and risk models are reviewed in Appendix II.

2. AETIOLOGY OF HUMAN CANCER

2.1. INTRODUCTION

Cancer is one of the major causes of morbidity and mortality worldwide. It is recognised that human cancer has multiple causes and many different mechanisms of carcinogenesis have been postulated. Some of the many factors which may cause cancer exist naturally, e.g. solar ultra-violet radiation, and others may be related to occupation and lifestyle, such as smoking, alcohol consumption or sexual behaviour. This Section summarizes the current theories in cancer development, some of the factors which are known to cause cancer, including ionizing radiation, and the interaction between some of these carcinogenic factors.

2.2. STAGES IN CANCER DEVELOPMENT

It is generally accepted that there are at least three separate phases in cancer development; initiation, promotion, and progression. The overall timescale varies with different tumours and between individuals, and the phases are not fully defined separate entities but theoretical sequences in cancer induction [1]. The current concept is that in the initiation phase an agent could by a single event evoke a change in a DNA target in one cell, which could be a random point mutation, a gene change in expression or a gene rearrangement, such as a chromosomal translocation. However, this event alone would not be sufficient to induce a malignant change but requires the subsequent contributions from promotion and progression. Promoters are thought to be agents that have low carcinogenic activity and require multiple or chronic exposures to trigger the initiated cell to undertake further change in the carcinogenic process. The final phase is progression where the malignant cells divide in a variable fashion to produce tumours, which may enlarge in size and even metastasize to other parts of the body. The last two phases are likely to have a bearing on the length of the latent period between an initiating event and the clinical manifestation of the tumour, and could explain, in part, the wide variation in the time course for different tumours and the variability between the same tumour types in individuals.

2.3. FACTORS CAUSING CANCER

Some cancers may arise "spontaneously" because the causative agent is not yet known. Such cancers might be defined as "naturally occurring" and it would be very difficult to assign a specific cause to them. There are a large number of agents known to induce cancer, ie. carcinogens, to which humans may be exposed knowingly and unknowingly during their lifetime. The former may include those encountered at work, during medical treatments or related to social lifestyles, such as diet, tobacco smoking etc. The latter ones can be associated with general environmental pollution or with natural sources, eg solar radiation and ingestion of foodstuffs contaminated by aflatoxins. There are difficulties in establishing a specific cause for a particular cancer in an individual because of the variable and possibly multiple nature of their lifetime exposure to known carcinogens and the variable individual susceptibility to each agent or circumstance. A selection of some of the known carcinogens and carcinogenic activities or circumstances to which humans may be exposed are presented in Table I.

It can be seen from Table I that an individual may be exposed to a wide variety of known or highly likely carcinogens or circumstances throughout their lifetime knowingly or unknowingly. Many other factors are thought to be carcinogenic, such as cooking products,

viruses and parasites. Social factors such as general lifestyle, which would include housing and sexual activity, could significantly affect an individual's chance of exposure and so the probability of developing cancer. This whole subject is further complicated by geographical and ethnic variations in so called natural cancer incidence rates. Correlations between exposure to these factors and cancer induction is primarily established on the basis of epidemiological studies where accurate individual exposure quantification can be made.

TABLE I. A SELECTION OF CARCINOGENS, ACTIVITIES, EXPOSURE CIRCUMSTANCES AND CANCER SITES

Carcinogen	Exposure or circumstance				Cancer site(s)
	Occupational	Medical	Social	Environmental	
Benzene	+				Bone marrow
Asbestos	+			+/-	Lung, pleura and peritoneum
Arsenic	+	+			Lung, skin
Ionizing radiation	+	+		+/-	Marrow, bone, lung and others.
Ultra-violet radiation	+		+		Lip, skin
Polycyclic hydrocarbons	+	+		+/-	Skin, scrotum, lung
Alkylating agents		+			Marrow, bladder
Steroids		+			Liver
Alcohol			+		Mouth, pharynx, oesophagus, liver
Tobacco smoking			+		Mouth, larynx, lung, oesophagus, bladder
Sexual behaviour (virus)			+		Cervix uteri
Overnutrition (causing obesity)			+		Endometrium, gall bladder
Hepatitis B (virus)	+/-		+	+	Liver
Aflatoxin				+	Liver
Population mixing (virus)				+/-	Marrow, Burkitt's lymphoma
Air pollution*				+/-	Various

(Adapted from Ref. [2].)

Notes:
+ Definite carcinogenic activity or circumstance.
+/- Probable carcinogenic activity or circumstance.
* Assumed from known contents of pollutants, e.g. arsenic, polycyclic hydrocarbons.

Diet can also modify the effectiveness of carcinogenic factors. There is a relationship between fat intake and mammary cancer. Other cancers such as cancer of the breast, ovary, and endometrium may show hormone dependence and are less common in women who have had children early in life than those who have had no children.

The relative importance of environmental and genetic factors can be identified by analysis of cancer incidence rates in populations that have migrated. Black Americans have cancer incidence rates that are much more like those of white Americans than those of black populations in West Africa [2].

The role of infection in carcinogenesis appears to be primarily associated with viruses. Viruses are known to become integrated into genetic material and to be able to modify the behaviour of cells.

Chronic obstructive pulmonary disease was found to be the second factor after smoking which increased lung cancer incidence among workers with plutonium-239 intake in the first Russian nuclear enterprise [3]. However, the contribution of each of these factors still requires clarification.

2.4. INTERACTION OF CARCINOGENIC AND OTHER FACTORS

Three types of interactions are important in considering cancer induction from combined exposures to carcinogenic and other agents. When the end effect of the combined action equals the sum of the two agents acting independently, the resulting situation is one of "additivity". When the effect of the combined action exceeds the sum of the two the situation is one of "synergism". When the effect of the combined action of the two is less than the sum of them the situation is termed "antagonism".

The degree of synergism can vary and in general the interaction will not multiplicate by more than a factor of ten (see Table II). Examples of these effects are:

- Additivity

  Studies have shown that alcohol consumption and smoking tobacco have an additive effect in the causation of pharyngeal, and oesophageal cancer [4, 5].

- Synergism

  A synergistic effect has been observed with the combined occupational exposure to asbestos and tobacco smoking in the incidence of lung cancer [6, 7].

- Antagonism

  There are no known situations where two carcinogens act antagonistically in humans. There are several anti-oxidant agents which theoretically might have anti-carcinogenic effects in humans but the actual quantification remains unknown. There is strong evidence to suggest that dietary factors may reduce cancer risk, notably ß-carotene in certain vegetables, where low levels increase the risk factors for several cancers [2]. Substances such as selenium, dietary fibre, and some vitamins and pro-vitamins are also thought to be anticarcinogens [8].

- Radiation carcinogenesis

  There are a large number of agents which have been identified as being carcinogenic in man. While it is not possible to give precise estimates of probability of cancer induction for an individual has been suggested that over 98% of cancer is due to causes other than radiation [9]. Occupational exposures to radiation will usually be less than a radiation worker's overall lifetime exposure from natural and medical sources. Workers may also be exposed to other carcinogens, both at work and at home, and so assigning a probability that a given tumor was induced by radiation requires very careful analysis.

TABLE II. THE RELATIVE RISK OF LUNG CANCER DUE TO EXPOSURE OF CIGARETTE SMOKE OR ASBESTOS OR BOTH

		ASBESTOS	
	Exposure	NO	YES
CIGARETTE SMOKE	NO	1 (reference)	5
	YES	10	50

(Derived from Ref. [10].)

3. RADIATION AS A CAUSE OF CANCER

As has been seen, ionizing radiation can cause cancer, although it is not a major cause and does not rank high as a public health hazard. Nevertheless, cancer induction following low doses has been assumed to take place [11], and as such constitutes a potential hazard facing workers exposed to ionizing radiation. It is the purpose of this report to examine this risk and to attempt to quantify it. Since chronic lymphatic leukaemia (CLL) and Hodgkin's Disease are not considered to be radiation induced [11], they have been excluded. In addition, there are a number of cancers for which inadequate data on radiation induction exists for reliable risk estimate derivation.

Epidemiological data are discussed in Section 4.

3.1. IONIZING RADIATION

Ionizing radiation may be high energy electromagnetic radiation (X and gamma rays) or energetic sub-atomic particles such as alpha and beta particles and neutrons. X and Gamma rays interact with matter and tissue according to their energy, and although there are different mechanisms, they all produce positively and/or negatively charged ions which then interact with the absorbing matter to produce physicochemical changes. The energy of these electromagnetic radiations will also determine their penetration, higher energy photons penetrating further than low energy ones. When they do interact with tissues and cells, energy is deposited within the tissue. These physicochemical changes lead through mutations to malignant cell transformations.

Energetic particles interact with matter based not only on their energy, but also on other characteristics such as charge and mass. For example beta particles, which are electrons with a single negative charge and a low mass, will tend to penetrate further than alpha particles whose charge is double but positive and whose mass is very much higher. Thus alpha particles do not constitute a significant hazard as an external source, but do when taken into the body as alpha emitters where they can irradiate adjacent cells in, for example, the bronchial epithelium. Neutrons, because of their absence of electrical charge, produce ionization indirectly and are much more penetrating.

The main feature of ionizing radiation is that it has sufficient energy to break chemical bonds and ionize atoms and molecules, producing an ion pair. These ions are charged and capable of causing further ionization and energy deposition leading to physicochemical changes in cellular constituents.

Some of these changes may be of no biological consequence and others may be repaired, but there is a finite probability that damage may cause cell death or unrepaired damage to vital cell constituents. The basic concept of absorbed dose is a measure of the mean energy absorbed by unit mass of tissue, and the absorbed dose in Gray (Gy) is equal to the deposition of one Joule (J) of energy in 1 kilogram (kg) of tissue. In general, the greater the dose, the greater is the likelihood of a biological effect being observed. Energy is deposited along the path of ionizing radiation as it traverses human tissue in the form of ionizations. The average deposition of energy per unit length is called the linear energy transfer (LET).

Charged particles tend to have higher LET values than X or γ rays. Different types of radiation have different observable radiation effects which depend on the spatial distribution of this energy deposition as the probability of stochastic effects depends on the type of the radiation. ICRP has introduced a radiation weighting factor (W_R) which may range from 1 to 20 for different types of radiation. Photons are assigned a W_R of 1 (low LET) and alpha particles 20 (high LET). These radiation weighting factors are used to convert the absorbed dose in Grays to an equivalent dose in Sieverts (Sv) when there is an energy absorption of the ionizing radiation in living tissue.

3.2. THE CELL TARGET

It is generally accepted that for carcinogenesis, the cellular DNA of the genome is the critical molecule. Damage to this molecule leading to cancer can be caused through the direct ionization by radiation or by its indirect action in the formation of free radicals in water in close proximity to the genome. These free radicals may then interact with DNA. This indirect effect accounts for about two thirds of the biological effect in case of low LET radiation, but the direct effect predominates with high LET radiation [11].

The human genome is composed of DNA contained largely in the cellular chromosomes of which there are 23 pairs. The total number of genes is unknown, but it is known that the size of genes may well vary by as much as a factor of 200 [11]. At cell division, the chromosomes are duplicated and shared between the two daughter cells. The genome can also undergo mutation which can range from small point mutations to major chromosome aberrations. Some of these mutations are lethal to cell survival and some may be repaired, but some may also be compatible with continued replication. In some medical conditions, such as Ataxia telangiectasia and Franconi's syndrome, there exist genetic defects in cell repair mechanisms which produce an increase in individual sensitivity to ionizing radiation. At high doses, cell death will predominate leading to organ malfunction, whose severity is dependent on the dose. These are called "deterministic effects", but with the survival of the individual, an increased risk of other effects, called "stochastic effects" (such as cancer) will occur. With deterministic effects, cause and effect can be clearly shown. However, due to the random nature of the interaction of radiation with matter, the establishment of a cause for stochastic effects is not possible and the inference of cause can only be based on the increased probability of the occurrence of the observed effect. Where dose is lower (as is likely in occupational exposures), only stochastic effects are seen. The severity of stochastic effects is not dose dependant as it is with deterministic effects. An increase in dose produces an increase in the probability of a stochastic effect but not in the severity of the effect.

3.3. STOCHASTIC EFFECTS

These effects result from an alteration in the genome of a cell, which, in the case of cancer gives rise to a clone of uncontrolled, rapidly dividing cells. Various mechanisms might be involved in mutation of the DNA. These may include the activation of an oncogeny (a cancer-causing gene), the inactivation of a tumour-suppressor gene or the loss of function of a repair-mutator gene [12].

The overt expression of a cancer may require the intervention of some other promotional agent, and this may account for some of the delay in the clinical appearance of the cancer known as the latent period. Other factors which may influence latency include the doubling time of the tumour growth and occasionally hormone dependence of specific tumours. The expression of stochastic effects due to radiation is random in nature, only increasing in frequency in a population with increasing dose. A radiation induced cancer cannot be distinguished from a cancer caused by any other process, with the result that reliance has to be placed on statistical evidence and risk models to infer a radiation cause.

3.4. EVIDENCE FOR THE RADIATION INDUCTION OF CANCER

There is no firm evidence from human low-dose epidemiological studies which unequivocally demonstrates an increase in cancer incidence. This may well be due to the fact that the size of the exposed population required to demonstrate such an increase would be so large that it is not feasible to manage. Nevertheless, numerous studies of humans exposed to high doses have shown an increased cancer incidence due to that exposure. Some of these are mentioned in the next section. The problem arose when an attempt had to be made to assess the effects of low doses, especially for occupational exposure. The ICRP has recommended that the risk be extrapolated on a dose proportional basis from high to low doses and dose rates. This assumption has formed the cornerstone of radiation protection principles for many years and has led to the development of current risk estimates, which are widely accepted by Member States.

3.5. RISK ESTIMATES

Quantitative estimates of the cancer risk to humans from radiation exposure cannot be made without human exposure data, as inter-species extrapolation is not reliable [11]. This necessitates the use of epidemiological studies of exposed groups. By far the largest group that has been studied systematically is that of the Japanese atomic bomb survivors. Other groups such as women treated with ionizing radiation for carcinoma of the cervix [13], and patients treated for ankylosing spondylitis [14] provide additional data for the development of risk estimates. Much of the available epidemiological data is far from ideal for risk estimation in the occupational exposure setting and various assumptions need to be made to extrapolate from these data. These include:

(a) Dose

Most studies showing effects involve high doses and dose rates which then have to be extrapolated down to occupational exposures which usually involve lower doses and dose rates which are considered to be less effective in inducing cancer. For this reason, a dose and dose rate effectiveness factor (DDREF) of 2 for low LET radiation was suggested by ICRP [15] in estimating occupational risk exposure from such studies.

(b) Quality of epidemiological studies

The quality of data also influences the acceptability of an epidemiological study. Thus careful attention needs especially to be taken to ensure complete follow-up, accurate exposure information and comparability of control and exposed groups. Large sample sizes are needed to establish statistical correlations, especially for low risks. Modifying or confounding factors need to be minimized and taken into account. Thus other carcinogen exposure such as smoking cannot be ignored.

In order to develop long term risk estimates, the study population should ideally be followed for its life span. However, it is not possible to wait until this happens, as interim risk estimates are needed. In order to do this, assumptions have to be made and models developed that reflect the known data and which, at the same time, take into account the uncertainties.

The transfer of such derived risk estimates to other populations which differ in ethnic background, age and sex, needs to be undertaken with great care. Life style features may also vary from population to population and can effect cancer incidences.

(c) Dosimetry

The accuracy of the dosimetry involved in large epidemiological studies is also a potential source of error and needs to be carefully evaluated. Recent risk estimates [12] are based largely on the Japanese Bomb Survivor data, which included approximately 93 000 people who were in the two cities at the time of explosions. One drawback to the use of these data for risk estimates at low dose and dose rates, is the contribution from neutron exposure. Estimates of the total exposure dose to the A-bomb survivors were revised in 1986 [16] which along with the appearance of more cancers in the ageing survivors led to a revision upwards of the risk estimates.

These data only show a clear evidence of an increase in solid cancer incidence in the 0.2–0.5 Sv dose range and above, and the instantaneous nature of the exposure has to be adapted to the more prolonged exposures normally seen in occupational environments. Nevertheless, these data were considered to be the best available and were used as the basis for ICRP's [15] nominal probability coefficient of 4.8×10^{-2} Sv^{-1} for cancer induction in adult workers. Risk estimates have also been developed for cancers of some individual organs. These factors are discussed further in Sections 5 and 6.

3.6. FACTORS INFLUENCING RADIOSENSITIVITY AND MODIFICATION OF EFFECTS OF EXPOSURE BY OTHER FACTORS

Susceptibility to the carcinogenic effects of radiation is summarized in BEIR V, and can be affected by a number of factors such as genetic constitution, sex, age, physiological state, smoking habits, drugs, and various other physical and chemical agents [11]. The genetic basis of some diseases including increased cancer susceptibility is becoming more clear. For example, it has recently been shown that Ataxia Telangiectasia, a genetic disease with many manifestations, is due to a mutated gene [17]. The full expression of this disease, including enhanced cancer susceptibility, results from homozygous mutated genes on chromosome 11. In addition, the heterozygous carriers, who do not express the full-blown disease, are known to be subject to a cancer incidence, especially for breast cancer, in excess of the normal population. This mutation is thought to act through inactivation of repair mechanisms. The

mechanisms through which these factors influence the radiosensitivity are, however, not well understood. They depend on the particular type of cancer, the tissue at risk, and the specific modifying factor under consideration.

Cancer rates are highly age dependent and, in general, increase rapidly in old age. The expression of radiogenic cancers varies with age in a similar way, so that the age-dependent increase in the excess risk of radiogenic cancer is conventionally expressed in terms of relative risk; that is, the increased risk tends to be proportional to the baseline risk in the same age interval. However, in some cases such as breast cancer, the change in the baseline cancer rate with age is more complicated. For lung cancer the situation is also not simple. Smoking and prolonged exposure to inhaled alpha-particle emitters interact in a multiplying fashion, or nearly so, this is said then to be a multiplicative effect.

For lung cancer and most other non-sex-specific solid cancer, it is unclear how a person's sex affects the risk of radiogenic cancer. In general, baseline rates for such cancers in males exceed those in females, possibly because of increased exposure to carcinogens and promoters in occupational activities and lifestyle factors, such as increased smoking and consumption of alcohol. While sex specific excess rates of cancer can generally be modelled adequately as being proportional to the corresponding sex-specific baseline rates; in many cases an additive excess risk model fits the data equally, that is, the number of radiation-induced cancer per unit dose is nearly the same in both sexes. For example, as it is known, the carcinogenic process includes the successive stages of initiation and promotion. The latter phase, appears to be particularly sensitive to cigarette smoking.

4. CHOICE OF RISK MODELS

4.1. INTRODUCTION

Until the 1980s two fairly simple models for describing and calculating radiation-induced cancer risks were used by national and international committees such as the Committee on the Biological Effects of Ionizing Radiation (BEIR) [11], the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [1, 39] and the International Commission on Radiological Protection (ICRP) [15]. The first is the *time-constant absolute (or additive) risk projection model* which assumes that after some latent period the excess cancer risk is constant. The second is the *time-constant relative (or multiplicative) risk projection model* which assumes that following administration of a dose of radiation after some latent period the cancer rate rises in a manner proportional to the underlying cancer risk. Largely as a result of extra years of follow-up in the Japanese bomb survivors, it became clear that the relative risk model fitted the solid cancer data much better than the absolute risk model. For this reason ICRP [15] and most other scientific committees tend to use the relative risk model rather than the absolute risk model for projecting solid cancer risks to the end of life.

4.2. EFFECT OF AGE AT EXPOSURE AND TIME SINCE EXPOSURE ON SITE SPECIFIC CANCER RISK

For solid cancers there is evidence, discussed below, that relative risks might diminish with time after exposure. For this reason one is led to fit a *generalised relative risk model* in which the cancer rate t years after exposure for sex s following exposure at age e to a dose D of radiation is given by:

$$r_o\,(a,\ s)[1\ +\ F(D)\alpha(t,e,s)] \qquad (1)$$

where $r_o\,(a,\ s)$ is the cancer rate in the absence of irradiation, i.e. the baseline cancer rate, $a = t + e$ is the age at observation (attained age) of the person and $F(D)$ is the function determining the dose dependency of the cancer risk, to be discussed later. The expression $\alpha(t,\ e,\ s)$ describes the modification to the excess relative risk $F(D)$ as a function of time since exposure t, age at exposure e and sex s.

For leukaemia neither the time-constant additive risk model nor the time-constant relative risk model fits well. For reasons largely of ease of interpretation, Preston and colleagues [36] present most of their published analyses of the Japanese atomic bomb survivor leukaemia incidence dataset using a corresponding *generalised absolute risk model*, in which the cancer rate t years after exposure for sex s following exposure at age e to a dose D of radiation is given by:

$$r_o\,(a,\ s)\ +\ F(D)\beta(t,e,s) \qquad (2)$$

The expression $\beta(t,\ e,\ s)$ describes the modification to the excess absolute risk $F(D)$ as a function of time since exposure t, age at exposure e and sex s.

However, given appropriate forms of the modifying functions $\alpha(t,\ e,\ s)$ and $\beta(t,\ e,\ s)$ of the relative and absolute risk respectively, equivalently good fits to the leukaemia incidence dataset were achieved using both generalised relative and generalised absolute risk models [36]. It is to some extent arbitrary which of these two models one uses. The modifying functions employed in modelling leukaemia incidence or mortality, whether they be in relation to the absolute risk or to the relative risk must necessarily allow for large changes in the absolute or relative risks with time and age, in accordance with what has been observed in the Japanese atomic bomb survivor data [16, 36] and in various other datasets [11, 39] (and see also Appendix I).

There is substantial evidence that the excess relative risks for most cancer sites decrease with increasing age at exposure [39]. As discussed in Appendix I, the evidence for variation in relative risk with time after exposure is more mixed. Certainly for leukaemia there is little doubt that the excess relative risk significantly decreases with increasing time after exposure within a few years of exposure [23, 39]. At least for certain cancers of the digestive system and for lung cancer there is some evidence that relative risks decrease with increasing time after exposure [23, 40], and as is discussed in Appendix I. There are strong indications that the relative risks of solid cancer for those irradiated in childhood decrease with increasing time after exposure, from about 25 or more years after exposure onwards [16, 25, 26, 38]. Apart from the cancer sites already discussed, there is no very convincing evidence for time variations in the relative risk of solid cancer following irradiation in adulthood [25, 26, 38].

4.3. EFFECT OF DOSE AND DOSE RATES ON SITE SPECIFIC CANCER RISK

It has been customary [39] to model the dose-response function $F(D)$ in fits to epidemiological data by the following linear-quadratic expression:

$$F(D) = D + \gamma D^2 \quad (3)$$

There is significant curvilinearity in the dose-response for leukaemia in the Japanese atomic bomb survivors [35], although for solid cancers there is no evidence for anything other than a linear dose-response in the Japanese cohort [35] or in any other group [23] (discussed further in Appendix I). It should be noted that as well as modifications in effectiveness (per unit dose) relating to alterations in the total dose there are also possible variations of effectiveness as a result of dose fractionation and dose-rate effects [1]. Therefore, although for cancers other leukaemia there is generally little justification for assuming anything other than a linear dose-response, i.e. $\gamma = 0$, it may nevertheless be justifiable to employ a dose and dose rate effectiveness factor (DDREF) other than 1. (The DDREF is the factor by which one divides risks for high dose and high dose-rate exposure to obtain risks for low doses and low dose-rates.) UNSCEAR [39] and the BEIR V Committee [11] employed a linear-quadratic model for leukaemia fitted to the Japanese atomic bomb survivor cancer incidence and mortality datasets respectively (the models are further described in Appendix II), and therefore a DDREF of 1 was used. A contrasting approach was adopted by the ICRP [15], who used various linear models for leukaemia fitted to the Japanese atomic bomb survivor mortality data; because of this using a DDREF of more than 1 was justified. The ICRP [15] recommended that a DDREF of 2 be used together with models linear in dose for all cancer sites, on the basis largely of the observations in various epidemiological datasets. UNSCEAR [39] and BEIR V [11] used linear models for all cancers other than leukaemia. UNSCEAR [39] recommended that a DDREF of no more than 3 be used in conjunction with these linear models.

4.4. CONSEQUENCES OF CHOICE OF MODEL FOR PC CALCULATIONS

The evidence discussed above indicates that time-constant relative risk models may not provide a perfect description of solid cancer risk, although they provide a better fit than time-constant absolute risk models, while for leukaemia both the time-constant relative and time-constant absolute risk models provide a very poor fit to the data. To this extent one is compelled to consider generalised relative and absolute risk models of the sort discussed above. Which of the generalised relative or absolute risk models one uses is to some extent arbitrary. For ease of PC calculations the generalised relative risk model is clearly to be preferred since it does not require knowledge of baseline cancer mortality and incidence rates.

4.5. LATENT PERIODS

Although it is often observed that a significant excess risk of radiation-induced solid cancer is not seen until at least 10 or more years after exposure [63], a radiation-related increase in solid cancer mortality is apparent in the Japanese atomic bomb survivor cohort during the first five years of follow-up, 5-10 years after the bombings (ERR = 0.24 shielded kerma/Sv, 90% CI 0.05-0.48) [16].

For leukaemias there is evidence of a much shorter interval between irradiation and the appearance of a significant excess risk. In the International Radiation Study of Cervical Cancer patients (IRSCC) — which consists of a combined cohort from various cancer registries of patients followed up for second cancer after therapeutic irradiation for cervical cancer [20] — there is a significant excess risk of acute non-lymphocytic leukaemia in the period 1–4 years after first treatment; a significant increase in risk between 1 and 5 years after

treatment is seen in the case-control study assembled from within this cohort [19]. In the UK ankylosing spondylitis patients there is a significant excess risk even in the period up to 2.5 years after first treatment [14]. This rapid rise in risk shortly after ionizing radiation exposure is paralleled in many other irradiated groups [39] (discussed further in Appendix I).

Carcinogenesis may be described by quasi-biological or mechanistic models, in which cancer is assumed to result from the accumulation of a sufficient number of critical mutations (as discussed in Section 2). Among the better known models of carcinogenesis that have been proposed are the so-called multi-stage model of Armitage and Doll [18] and the so-called two-mutation model of Moolgavkar and colleagues [31]. Either of these mechanistic models, and various generalisations of them also [24], predict that soon after exposure the excess risk would begin to increase [24, 25, 27, 28]. In an individual the latent period should not be regarded as a well-defined interval, in as much as given a sufficiently large group of persons who are exposed to a sufficiently large dose of radiation, an arbitrarily small latent period might be detected.

4.6. EFFECT OF SEX ON SITE SPECIFIC CANCER RISK

The Japanese atomic bomb survivor dataset provides clear evidence of sex differences in the excess relative risks of solid cancers. For solid tumours, the excess relative risk for females is generally about twice that for males [16]. However, the ratios of naturally occurring age-specific cancer rates in females in Japan are about half those of for males, which implies that absolute excess risk are roughly equal for males and females. The joint analysis of the Japanese atomic bomb survivor mortality data for three broad categories of cancer (digestive system, respiratory system and other nonspecific solid tumours) by Pierce and Preston [34] adds support to the hypothesis that sex effects in the excess relative risks largely reflect differences in sex-specific rates of normally occurring cancer.

For solid tumours analysed as a group, within the Japanese atomic bomb survivor incidence dataset the excess relative risks for females are larger than those for males [38]. However, in accordance with the hypothesis described above, the excess absolute risk sex ratios are generally closer to one than are the excess relative risk ratios. Results for cancers of the liver and thyroid [38] and for leukaemia [36] appear to deviate from this pattern. For liver cancer the excess risks, both relative and absolute, appear to be substantially lower among females than among males despite the fact that in the Japanese atomic bomb survivor dataset, as in other (unexposed) populations [33], naturally occurring liver cancer rates for males are higher than those for females [38].

In the Japanese atomic bomb survivor dataset and in other (unexposed) populations [33], thyroid cancer occurs only about one third as often in males as in females. Despite the difference in background rates, age specific excess relative risk estimates are not significantly different between the two sexes [38]. The sex ratio seen for leukaemia baseline rates is about the same as that seen for other cancer types, but the sex-specific excess relative risks are similar.

4.7. TRANSFER OF RISK ESTIMATES BETWEEN POPULATIONS

The form of model that one uses for projection over time is to some extent associated with the form of model that one employs for projection between populations. For example, if one uses the relative risk model **(1)** for fits to some irradiated population with underlying cancer rate $r_O(a, s)$, and one wishes to estimate risks for another population with underlying

cancer incidence rate R_O *(a, s)*, then the ratio of the excess cancer rates to the underlying cancer rates in the two populations might be assumed to be identical, i.e. there is a *multiplicative transfer* of risks, in which case, under the same circumstances as above, cancer rates in the second population might be assumed to be given by:

$$R_o\ (a,\ s)[1\ +\ F(D)\alpha(t,e,s)] \tag{4}$$

Alternatively, if one uses the additive risk model (2) for fits to some irradiated population with underlying cancer rate r_O *(a, s)*, and one wishes to estimate risks for another population with underlying cancer incidence rate R_O *(a, s)*, then the excess cancer rates in the two populations might be assumed to be identical i.e. there is an *additive transfer* of risks, in which case, under the same circumstances as above, cancer rates in the second population might be assumed to be given by:

$$R_o\ (a,\ s)\ +\ F(D)\beta(t,e,s) \tag{5}$$

Despite the relatively large quantity of data on radiation risks, the question of how to apply risk estimates derived for one population to a different population remains unanswered. The data that are available suggests that there is no simple solution to the problem [39]. For example, there are weak indications that the relative risks of stomach cancer following radiation exposure may be more similar than the absolute excess risks in populations with different background stomach cancer rates [39]. The breast cancer relative risks observed in the most recent analysis of the Japanese atomic bomb survivor incidence data [38] are much higher than those seen in various other datasets [21, 30, 37]. The observation that sex differences in solid tumour excess relative risk are generally offset by differences in sex-specific background cancer rates might suggest that absolute excess risks are more similar than excess relative risks.

Taken together, the above considerations suggest that in various circumstances relative or absolute transfers of risk between populations may be recommended, or indeed the use of some sort of hybrid approach, such as that which has been employed by Muirhead and Darby [32]. Mechanistic considerations imply that the interactions between radiation and the various other factors which modulate the multi-stage process of carcinogenesis may be complex [11], so that in general one would not expect either relative or absolute risks to be invariant across populations.

For the purposes of modelling radiation-induced cancer risk in given various exposed populations such as the Japanese atomic bomb survivor population, both generalised relative and generalised absolute risk models provide equivalent goodness of fit. For ease of calculation of PC the generalised relative risk formulation is to be preferred. If a generalised relative risk formulation is employed then for all cancer types adjustments for age at exposure must be employed. For leukaemia adjustments to the relative risk for time since exposure must also be used. For solid cancers, only for digestive cancers and lung cancer as well as for those exposed in childhood is there strong evidence for the relative risk being non-constant. Latent period is not well defined and may vary considerably, but for purposes of PC calculation should not exceed 10 years for solid cancers and 2 years for leukaemias.

5. PROBABILITY OF CAUSATION

5.1. DEFINITION

As discussed in the preceding sections a radiation induced cancer is indistinguishable from one induced by other agents. Increased cancer risks associated with radiation exposure have been ascertained on the basis of epidemiological observations in exposed groups. However, in no case can it be proved that a particular cancer was due to an earlier exposure. The concept of the probability of causation (*PC*) has been developed to answer the question: if a person has been exposed to ionizing radiation and subsequently gets a cancer, what is the probability that the cancer was due to the earlier exposure? The *PC* was defined by the United States National Institutes of Health (NIH) Ad Hoc Committee [10] as the fraction of the risk at the age of occurrence for the given cancer that is attributable to the exposure, i.e.,

$$PC = \frac{\Delta r\ (D,\ t,\ e,\ s)}{r_0\ (a,\ s) + \Delta r\ (D,\ t,\ e,\ s)} \tag{6}$$

where $r_0(a, s)$ is the cancer rate for age a and sex s for the particular cancer type under consideration and $\Delta r(D, t, e, s)$ is the excess cancer rate due to exposure to a dose of radiation D at age e and time since exposure t ($= a - e$). The rate for a given cancer is the probability per unit time for a person of sex s and age a to develop the cancer.

The age and sex specific cancer rates are average values applicable to groups of a population. It is well known that the individual risk of cancer depends not only on the age and sex of a person but also on other individual characteristics such as dietary habits and genetic background. Such factors are presently not quantifiable and cancer rates are usually available from demographic data tabulated by age and sex, and so usually only these factors can be taken into account. This implies that in calculating the *PC* relating to a particular occurrence the individual characteristics (other than age and sex) of a person are ignored. Cancer rates when kept and published are usually collated nationally and by regions for a given calendar period.

However, for lung cancer the dependence of the spontaneous rates on smoking habits of an individual need to be considered since this is the principal cause for this cancer. However, despite of the overwhelming influence of smoking habits on lung cancer, quantitative scientific information on the possible synergism between smoking and radiation is scarce. One has therefore to rely on somewhat uncertain hypotheses.

It should be noted that the expression "probability of causation" is to some extent misleading since the probability of causation does not have all the properties of a probability in the mathematical sense. The development of cancer being a multi-step process, a number of factors are involved that do not act independently. This may be illustrated by considering the effect of smoking and radiation on lung cancer. It is estimated that the risk for lung cancer in a uranium miner exposed to 100 working level month (WLM) is roughly twice as high as the risk of a non-exposed person, i.e., the *PC* relating to the exposure is 0.5. On the other hand, a smoker has a tenfold risk compared with a non-smoker, i.e., the *PC* for a smoker dying from lung cancer is 0.9. Despite of this limitation, the probability of causation is still a useful notion that can be understood as the chance that a particular cancer was induced by radiation.

5.2. LIMITATIONS

In spite of the relative simplicity of the notion the calculation of *PC* is made difficult by various limitations in the present knowledge on radiation risk and in available demographic data.

Present estimates of radiation risks are based on a number of epidemiological studies. Radiation may be the carcinogenic factor that has been most intensely studied, nonetheless in most situations that might arise the present knowledge is far from sufficient to describe with adequate precision the variation of risk with time and age. Even more than with the calculation of the life time cancer risk resulting from radiation exposure, probabilities of causation have to be based on hypotheses that are at best assumptions, which have been accepted as reasonable by experts. This limitation may not be critical in many practical situations dealing with occupational exposures. For solid cancers even if radiation increases risk, high doses far above the present limits tolerated for workers are necessary to increase the risk significantly above the spontaneous risk. It is only for the high doses such as might have occurred in earlier working environments that high *PC* values are possible. However, this is not true for leukaemias. High relative risks may occur for these malignancies even at low doses because of the time pattern of the radiation-induced leukaemias in relation to the generally low base-line rates. The hypotheses used to calculate probabilities of causation need in this case to be considered carefully.

The PC calculation requires demographic data on cancer incidence. While reliable mortality data exist in most countries, this is not the case for cancer incidence, since frequently, for reasons of data confidentiality, legislation prevents cancer registries from being established. Existing incidence data from other countries cannot be automatically transferred or applied to a country without such data without further consideration, since there are significant differences in cancer incidence rates between countries and even within countries for a number of cancer sites. The use of cancer mortality instead of cancer incidence data is justifiable for sites with high lethality such as cancers of the stomach or of the lung. It is more questionable for cancer types where therapy methods are successful.

As discussed in Section 4, the analyses performed in recent years by numerous scientific committees [11, 15] of various datasets of radiation-exposed persons have shown that the time-constant relative risk model fits the solid tumour data better than the time-constant absolute risk model. As shown in Section 4, for many solid tumour sites there are insufficient data to justify using more elaborate models. *PC* values in those cases are then quite readily calculated. Equation (6) becomes:

$$PC = \frac{ERR\ (D,\ e,\ s)}{1\ +\ ERR\ (D,\ e,\ s)} \tag{7}$$

The term $\boldsymbol{ERR(D,e,\ s)}$ represents the excess relative risk in its usual dependence on age at exposure e and sex s. If $\boldsymbol{ERR(D,e,\ s)}$ can be written as $\alpha(\mathbf{e,\ s})\cdot\boldsymbol{D}$, the inverse of $\alpha(\mathbf{e,\ s})$ is then the doubling dose, i.e. the dose necessary to double the baseline rates.

For a few tumour sites there is enough information to justify the use of more complex models than the time-constant absolute or relative risk models. With more complex models, where either the absolute or the relative excess rates are not constant but depend on time after exposure, it becomes a matter of convenience whether one uses a relative or an absolute

model when fitting the data. This can be seen most clearly in the models used by the BEIR V committee [11] and by UNSCEAR [39] for leukaemia. For leukaemia, more than for any other radiation-induced tumour, the temporal pattern of the radiation-induced excess incidence appears to be independent of the baseline rates, as is discussed further in Section 4 and Appendix I. Nevertheless, if a generalised relative risk model is used in the analyses of the Japanese atomic bomb survivor cohort with relative risk coefficients that depend on time and age at exposure the fit can be as good as with a generalised absolute risk model [36].

These two facts, the lack of reliable demographic data on cancer incidence and the present tendency to describe the excess risk using relative risk models, justify the use of generalised relative risk models in which the probability of causation may be expressed as:

$$PC = \frac{ERR\ (D,\ t,\ e,\ s)}{1\ +\ ERR\ (D,\ t,\ e,\ s)} \tag{8}$$

where t $(= a\text{-}e)$ is the time after exposure to a radiation dose D at age e for sex s.

The German PC tables [41] have been based on such generalised relative risk models. The difficulty caused by the absence of cancer registries is not completely overcome by the use of relative risk models since one question remains unanswered, namely how the risk observed in a given population, mostly the Japanese population, should be applied to another population with different background rates. This has been discussed in more detail in Section 4. It should be noted that the decision to apply either the relative or the absolute risks observed in the Japanese bomb survivors to a European population may lead to significantly different values of the probabilities of causation for those sites with appreciably different base-line rates in the two populations. This again will not be critical as long as low doses are considered. For situations where the *PC* values approach significance one might have to make a choice that is deliberately in favour of the claimant. This would imply using different hypotheses for cancers with high or with low base-line rates in the Japanese population compared with European populations.

The choice of the dependencies on time, age and dose in Equations (7) and (8) has to be in agreement with models used by international committees. However, the models that have been used by various scientific committees to derive life-time risk estimates either for workers or for populations are not always suitable to the requirements of *PC* calculations. Ideally, the models used for PC calculations should incorporate smooth dependencies on variables such as time, age and dose to avoid the practical incoherences that could easily occur with the step functions used, for example, by the BEIR V Committee [11].

5.3. THE EXPRESSION OF THE PROBABILITY OF CAUSATION FOR MULTIPLE EXPOSURES

In most cases occupational exposures are received chronically over years. The question arises of the resulting risk at a later age. In the absence of any better knowledge it is assumed that the risk at a given age is the sum of the risks from each exposure, implying that each exposure acts independently. In other words, the PC is given by:

$$PC = \frac{\sum_i ERR\ (D_i, t_i, e_i, s)}{1 + \sum_i ERR\ (D_i, t_i, e_i, s)} \qquad (9)$$

where D_i, t_i and e_i are the dose, time since exposure and age at exposure for the i^{th} exposure. The same hypothesis was used by the NIH Committee that produced the first radioepidemiological tables [10].

6. SOURCES OF UNCERTAINTY

6.1. INTRODUCTION

The uncertainties that are included in the radiation induced cancer risk estimation and also in the probability of causation calculations are many and fundamental. A first approach for quantification of the uncertainties was developed by NIH [10] and the BEIR V Committee [11]. However, ICRP [15] concluded that it was very difficult to achieve, in any precise way, a satisfactory measure of overall uncertainty in the risk estimations especially for low dose exposures. Therefore, only general outline about uncertainties will be given in this section.

6.2. EPIDEMIOLOGY

While epidemiological studies provide the primary data on the association between the induced cancer in man and exposure to ionizing radiation, certain limitations are inherent in such studies, due in part to the observational nature of epidemiology. So in interpreting epidemiological results it is important to be aware of the important limitations:

(a) the outcome of interest cannot be studied directly in most cases or with the desired precision;

(b) randomization procedures can not be used to ensure the absence of undesirable systematic differences between those exposed at different levels; and

(c) studies cannot usually be repeated at the command of the investigator.

6.3. EXTRAPOLATIONS

Risk estimates are strictly only applicable to the populations under study in specific circumstances. So extrapolations have to be applied to the transfer of these risks to other populations groups. The extrapolations that are most frequently required are:

(a) The extrapolation from the limited time of observation of the epidemiological study to life time risk estimations. No single large cohort has yet been followed throughout its entire lifetime, so that the lifetime risk cannot be determined by observation.

(b) The data are most incomplete for those who where exposed at young ages. If a time dependent relative risk model for solid cancers is adopted, uncertainty can be due to variation with time in the relative risk, especially for persons who were young at the time of exposure, and after intervals of 35 years or more.

(c) The extrapolation from high doses (generally above 1 Sv) and high (instantaneous) dose rates prevailing in the majority of epidemiological studies to the low doses and low dose rates which typically occur in the occupational environment could lead to uncertainties.

(d) The absence of a satisfactory theory of radiation carcinogenesis to validate the choice of mathematical functions used to perform the calculations leads to considerable uncertainty to those risk coefficients derived for the low-dose range.

6.4. DOSIMETRY

In the case of external radiation the equivalent dose to the relevant tissue is generally an average over the target organ. This is the quantity usually employed for risk estimations for organ specific cancer. In many cases the organ dose estimates arising from diagnostic and therapeutic irradiation are often uncertain and are very difficult to reconstruct and describe with precision. Average values may be fairly accurate, but individual doses are highly variable.

The dosimetry for the most important group of the A-bomb survivors has been revised in recent years. Various attempts have been made to predict the extent to which the next generation of dose estimates will change previously calculated risk coefficients.

The relative uncertainty in the measurement of doses near background levels is particularly large. An additional problem in estimating very low doses occurs because of the need for adjustment for background exposure, which is often accomplished by subtracting readings from control dosemeters. For personnel with very little or no recorded occupational dose, the methodology of dose estimation may contribute to uncertainties. If positive results for unexposed workers are recorded and are not compensated by substraction of negative results, cumulative doses for workers with little or no occupational dose will tend to be overestimated.

6.5. AVERAGE RADIOSENSITIVITY

Besides the extrapolations from high to low doses and from limited observation periods to lifetime risks there exists the problems of risk transfer from one population to an other. For example, the Japanese population is the most important source of data for radiation risk estimations, and for some types of cancer the only source. Since baseline cancer rates are different in other countries for many cancer sites, it is not clear whether cancer risks derived in one population are applicable to the other, and if so, whether relative or absolute risk models should be used for the transfer of risk estimations. The model may also vary from one cancer site to another.

When the absolute risk model is used for the transfer, uncertainty about the method to estimate the baseline incidence cancer rate in the relevant populations should be pointed out. When possible, age and sex-specific incidence rates for the general populations of the country should be obtained from a national registry or estimated from regional data. Uncertainty can arise from the use of data of a different country because incidence rates for certain sites can depend, inter alia on ethnic or life style variations. Moreover, as workers are often healthier than the general population so that their baseline cancer rates may differ from the rates of the population at large. Changes in cancer incidence rates over time can be another source of uncertainty.

The risk estimations are calculated from cancer incidence data in general populations, like the A-bomb survivors or special patient groups, however, there is usually no information about the dietary or hormonal status, genetic or differences in DNA repair capability, and other factors, such as immune status.

6.6. SEX

The effect of sex differences on risk estimates is not consistent and may lead to considerable uncertainties particularly in radiation induced breast and thyroid cancer, and leukaemia. In the case of lung cancer, data for women are not yet available in the literature for radon exposures and so assumptions have to be made.

6.7. CONTRIBUTION OF OTHER CARCINOGENS

The prevalence of carcinogens in man's environment and life style suggests that any individual with cancer following exposure to ionizing radiation will also have been exposed to many other carcinogens. The only competing risk factor for which exploitable data are published is for tobacco smoking in relation to lung cancer. The relative risk of lung cancer for smokers versus non-smokers is exceeded by very few other risk factors. However, the literature is unclear as to the exact nature of the interaction between ionizing radiation and smoking; the recent miner studies relying on more person-years suggest a nearby multiplicative relationship, while the A-bomb survivor data are perhaps more compatible with an additive effect of radiation and smoking.

6.8. TYPE OF RADIATION

Most data of epidemiological studies deal with low LET radiation. However, there are a few exceptions for example the risk estimations for bone cancer, which apply only to alpha radiation from radium, liver cancer in patients treated with Thorotrast (thorium) and estimates for lung cancer following exposure to alpha radiation from inhaled radon and radon decay products are provided by several miner studies.

The question of whether high-LET alpha radiation induces tumours other than those caused by low-LET radiation or more frequently than would be expected based on values of RBE or of the radiation weighting factor is not completely answered by the scientific information available so far.

7. EXAMPLES OF PC CALCULATIONS

Before calculating the probability of causation it is essential to establish that the radiation exposure was work related and that the exposure had a certain probability to cause the particular cancer. The cancer concerned should be known to be radiation inducible, for example, there is no evidence that chronic lymphatic leukaemia or Hodgkin's disease are induced by radiation.

It is also important to establish that the latency period between exposure and cancer diagnosis is consistent with those accepted as a result of epidemiological studies of radiation exposed populations. It takes at least two years for leukaemia and bone cancer and ten years for all other cancers to clinically manifest after exposure. Therefore, a lung tumour diagnosed five years after exposure, for example, is unlikely to be radiation induced.

The radiation exposure should normally be greater than that typically accumulated from natural background radiation.

Radiation induced cancer in tissues or organs other than those exposed would normally be exclude. Abscopal effects may possibly occur but are not proven in any literature.

For the calculation of the probability of causation the following data should be known:

- age at exposure;
- gender;
- external and/or internal dose to the whole body or individual organs;
- dose estimation (where there is inadequate formal dosimetry);
- the diagnosis;
- age at diagnosis; and
- other major risk factors besides radiation (smoking, exposures to solvents, medical radiation exposures, chemotherapy, etc.).

Several examples follow which are for illustrative purposes only and they should not be used in any compensation case.

EXAMPLE 1

A male is diagnosed with leukaemia at the age of 68 years. He received a single, uniform acute radiation dose to the red bone marrow of 100 mSv at the age of 43 years. Using the BEIR V model, what is the probability that this particular radiation dose was the cause of this leukaemia?

The BEIR V leukaemia model relevant to these particular circumstances
(E >20, T ≤25) is:
$RR = 1 + (0.243D + 0.271D^2) \exp(2.367)$

The man received a single acute dose of 100 mSv at the age of 43 years and was diagnosed with leukaemia 25 years later. Therefore,

$$RR = 1 + (0.243 \times 0.1 + 0.271 \times 0.1^2) \times 10.665$$

so that,

$$RR = 1 + 0.02701 \times 10.665$$
$$RR = 1.2881$$

and

$$PC = \frac{RR - 1}{RR}$$

$$PC = 22.37\%.$$

EXAMPLE 2

The same as Example 1, but the single acute dose of 100 mSv is received at the age of 40 years.

In this case, since the dose was received 28 years before the leukaemia was diagnosed, so that,

$$RR = 1 + 0.02701 \exp(1.638)$$
$$RR = 1 + 0.02701 \times 5.145$$
$$RR = 1.139$$

and

$$PC = 12.\ 20\%.$$

EXAMPLE 3

Same as Example 1, but the single acute dose of 100 mSv is received at the age of 35 years.

In this case, since the dose was received 33 years before the leukaemia was diagnosed, so that,

$$RR = 1 + 0.02701 \exp(0.0)$$
$$RR = 1 + 0.02701 \times 2.718$$
$$RR = 1.0734$$

and

$$PC = 6.84\%.$$

EXAMPLE 4

In this case, a single acute dose of 100 mSv is received at the age of 20 years and a leukaemia is diagnosed at the age of 45 years.

Now, because the age at irradiation is less than 21 years, and the leukaemia is diagnosed 25 years after the dose is received,

$$RR = 1 + 0.02701 \exp(2.380)$$
$$RR = 1 + 0.02701 \times 10.805$$
$$RR = 1.292$$

and

$$PC = 22.60\%.$$

EXAMPLE 5

Same as Example 4, but the leukaemia is diagnosed at the age of 33 years.

In this case, since the age at irradiation is less than or 21 years, and the time since exposure is less than 16 years,

$$RR = 1 + 0.02701 \exp(4.885)$$
$$RR = 1 + 0.02701 \times 132.29$$
$$RR = 4.573$$

and

$$PC = 78.13\%.$$

The above set of examples illustrate how the RR (and hence the PC) varies with age at exposure and time since exposure under the BEIR V leukaemia model. Although in all cases the single acute dose received is 100 mSv, the PC ranges from 6.84% when the age at exposure is greater than 20 years and the leukaemia is diagnosed more than 30 years since exposure, to 78.13% when the age at exposure is less than 21 years and the leukaemia is diagnosed less than 16 years since exposure.

Under the BEIR V leukaemia model, if a single acute dose of radiation is received before the age of 21 years and a leukaemia is diagnosed within 16 years of exposure, then a PC of 50% or more will be produced by a dose of 30.25 mSv or greater:

$$RR = 1 + (0.243 \times 0.03025 + 0.271 \times 0.03025^2) \exp(4.885)$$
$$RR = 1 + 0.0076 \times 132.29$$
$$RR = 2$$

and

$$PC = 50\%.$$

EXAMPLE 6

Same as Example 5, but using the UNSCEAR 94 leukaemia risk model instead of the BEIR V model.

The UNSCEAR 94 leukaemia model is an excess ABSOLUTE risk model in contrast to the excess RELATIVE risk model adopted by BEIR V.

The UNSCEAR 94 leukaemia model, under the particular circumstances of this case, is

$$EAR = 0.48 (D + 0.79 D2) \exp[-0.13(t - 25)]$$
$$EAR = 0.48(0.1 + 0.79 \times 0.1E02) \exp[-0.13(13 - 25)]$$
$$EAR = 0.246.$$

To obtain the RR (necessary for the calculation of the PC), the background absolute risk of leukaemia is required. The relevant background risk is provided in Appendix 2 of Preston et al. (1994):

for males:

$$B(s,a,g) = 0.91 \exp[-0.022(e-25) + 3.08\ln(a/50) + 1.22 \ln^2 (a/50)]$$

and for this particular case:

$$B = 0.91 \exp[-0.022(20-25) + 3.08\ln(33/50) + 1.22\ln^2(33/50)]$$
$$B = 0.349$$

so that

$$RR = (0.246 + 0.349) / 0.349$$
$$RR = 1.71$$

and

$$PC = 41.5\%.$$

This PC of 41.5% compares with the PC of 78.13% obtained using the BEIR V leukaemia model, and illustrates the different PCs which can be obtained when using different models.

EXAMPLE 7

Same as Example 6, but the single acute dose of 100 mSv is received by a female aged 20 years.

Under the UNSCEAR 94 leukaemia model, a different expression is now required for the excess absolute risk (EAR) because, unlike the BEIR V leukaemia model, the UNSCEAR 94 leukaemia model is sex-dependent.

$$EAR = 0.66 (0.1 + 0.79 \times 0.1^2) \exp[-0.07(13-25)]$$
$$EAR = 0.165$$

which has to be compared with the background rate for females:

$$B = 0.172$$

so that, in this case

$$RR = (0.165 + 0.172) / 0.172$$
$$RR = 1.96$$

and

$$PC = 49\%$$

which is higher than the equivalent exposure of a male of the same age, but still not as high as the PC obtained with the sex-independent BEIR V model.

EXAMPLE 8

Same as Example 6, a male receiving a dose of 100 mSv at the age of 20 years, but the leukaemia is now diagnosed at the age of 25 years.

In this case, the EAR is

$$EAR = 0.697$$

and the background rate is

$$B = 0.216$$

so that

$$RR = 4.227$$

and

$$PC = 76.3\%.$$

The equivalent calculation using the BEIR V leukaemia model would be exactly the same as the calculation set out in Example 5, and so under the BEIR V model the PC would be 78.1% which is comparable to the PC obtained using the UNSCEAR 94 model.

This example illustrates that the UNSCEAR 94 leukaemia model has the EAR continuously declining with time from 5 years after exposure, while the BEIR V model has a stepwise reduction in the ERR from 2 years after exposure.

EXAMPLE 9

Let us consider the case of a male diagnosed with leukaemia at the age of 68 years, as in Example 1, who received a dose of 100 mSv spread out evenly over a period of 10 years while he was aged 43 to 52 years.

In this case, each annual dose of 10 mSv makes a contribution to the relative risk of leukaemia under the BEIR V model of

$$RR = 1 + (0.243 \times 0.01 + 0.271 \times 0.01E02)\ \exp(2.367)$$
$$RR = 1 + 0.026$$

and the total ERR of the 100 mSv would be 0.26, giving

$$RR = 1.26$$

and

$$PC = 20.6\%.$$

The difference between this PC of 20.6% and the PC of 22.4% obtained in Example 1 (an acute exposure of 100 mSv at the age of 43 years) is entirely due to the linear-quadratic dose-response model built into the BEIR V leukaemia model.

EXAMPLE 10

Suppose now that the situation is the same as in Example 9 except that the chronic dose of 100 mSv is received evenly over the age range 38 to 47 years.

In this case, when the man is aged 43 to 47 years (that is, 25 to 21 years prior to the age at diagnosis) the contribution to the leukaemia ERR of each of the annual doses of 10mSv is the same as in the last example: 0.026. Therefore, the leukaemia ERR associated with the 50 mSv received over these 5 years is 0.13. However, for each of the annual doses of 10 mSv received in the age range 38 to 42 years (that is, 30 to 26 years prior to diagnosis) the ERR under the BEIR V model is given by

$$ERR = (0.243 \times 0.01 + 0.271 \times 0.01^2) \exp(1.638)$$
$$ERR = 0.013$$

so that the leukaemia ERR associated with this 50 mSv dose is 0.065, and the total ERR generated by the overall dose of 100 mSv is 0.13 + 0.013 = 0.143, to give

$$RR = 1.143$$

and

$$PC = 12.5\%.$$

Here we see the decreasing contribution to the PC of doses received at greater times before diagnosis. This dependency on time since exposure must be incorporated in the PC calculation through the use of the appropriate formula under the particular leukaemia model.

EXAMPLE 11

A male has received a dose of radiation of 5 mSv every year from the age of 18 years up until the age of 44 years when he is diagnosed with leukaemia. What is the PC of this leukaemia being due to this dose of radiation?

For those annual doses received before the age of 21 years:

The annual doses received at the ages of 18 and 19 years were received more than 25 years before diagnosis, and so the contribution to the ERR in each of these years is:

$$ERR = (0.243 \times 0.005 + 0.271 \times 0.005^2) \exp(0.0)$$
$$ERR = 0.0012$$

the annual dose received at the age of 20 years makes a contribution to the ERR of

$$ERR = 0.0012 \exp(2.380)$$
$$ERR = 0.0130$$

For those doses received in the age range 21 to 42 years, each annual dose makes a contribution to the ERR of:

$$ERR = 0.0012 \exp(2.367)$$
$$ERR = 0.0128$$

For doses received at the ages of 43 and 44 years, the doses make no contribution to the ERR of leukaemia because these doses were received within 2 years of the diagnosis of leukaemia and the BEIR V leukaemia model assumes a minimum latency of 2 years. Therefore, doses received within 2 years of a diagnosis of leukaemia cannot contribute to the PC under this assumption.

Therefore, the total ERR due to these annual doses is:

$$ERR = 2 \times 0.0012 + 0.0130 + 22 \times 0.0128$$
$$ERR = 0.297$$

giving

$$RR = 1.297$$

and

$$PC = 22.9\%.$$

EXAMPLE 12

A male is diagnosed with cancer of the colon at the age of 55 years. From the age of 18 years he received a dose of 5 mSv every year. What is the PC for this cancer being caused by this exposure to radiation under the relevant BEIR V model?

Colon cancer is addressed in BEIR V by the digestive cancer model, which, for males is:

$$ERR = 0.809\ D \exp(0.0)\ E \leq 25$$
$$ERR = 0.809\ D \exp -0.198\ (E-25)]\ 25 < E \leq 35$$
$$ERR = 0.809\ D \exp(-1.98)\ E > 35$$

For exposures received in the age range 18 to 25 years:

$$ERR = 0.809 \times 0.005$$
$$ERR = 0.004$$

so that the contribution to the PC for each annual dose in this age range is from

$$ERR = 0.004.$$

For doses received in the age range 26 to 35 years:

$$ERR = 0.004 \exp[-0.198\ (E-25)]$$

so that for doses received in these 10 years, the ERRs are:

$$ERR = 0.004 \times \exp(-0.198)$$
$$ERR = 0.004 \times \exp(-0.198 \times 2)$$
$$ERR = 0.004 \times \exp(-0.198 \times 3) \ldots \text{etc.}$$

For doses received in the age range 36 to 45 years, the ERR associated with each annual dose is

$$ERR = 0.004 \times \exp(-1.98).$$

For doses received within 10 years of diagnosis, the ERR is zero because for cancers other than leukaemia, a minimum latency of 10 years is assumed under the BEIR V model.

Therefore, the overall ERR due to this exposure to radiation is:

$$ERR = 0.004(8 + 0.820 + 0.673 + 0.552 + 0.453 + 0.372 + 0.305 + 0.250 + 0.205 + 0.168 + 0.138 + 10 \times 0.138)$$

$$ERR = 0.053$$

so that

$$PC = 5.0\%.$$

Note: a DDREF of 1 has been assumed in the above calculation. For cancers other than leukaemia (for which a DDREF of 2 is implicit in the model because of the linear-quadratic dose-response) a DDREF has to be explicitly included in the calculation if a DDREF other than 1 is required.

EXAMPLE 13

Same as Example 12, except that the UNSCEAR 94 model is to be used.

A specific colon cancer risk model is available in the UNSCEAR 94 report:

$$ERR = 0.54\ D \exp[-0.033(E-25)].$$

(Note that, unlike the UNSCEAR 94 leukaemia risk model, the UNSCEAR 94 risk model for cancers other than leukaemia is expressed as an excess relative risk model, and thus a background risk distribution is not required.)

Since the dose received in each year is constant (5 mSv), this expression for the ERR can be integrated over the age at exposure range 18 to 45 years:

$$ERR = 0.54 \times 0.005 \times ((\exp[-0.033(45-25)] / -0.033) - (\exp[-0.033(18-25)] / -0.033))$$
$$ERR = 0.061$$

so that

$$PC = 5.7\%$$

which is almost the same as the PC of 5.0% obtained using the appropriate BEIR V model.

EXAMPLE 14

A man is diagnosed with lung cancer at the age of 60 years. He received a single exposure of 10 WLM at the age of 25 years. Based on the lung cancer risk model developed by Jacobi et al., what is the probability that this lung cancer was caused by this exposure to radon? The smoking habits of the man may be ignored because smoking and radon are assumed to interact multiplicatively under this model (ie. the relative risk of lung cancer due to radon exposure is the same in the presence or absence of exposure to tobacco smoke).

The risk model is:

$$ERR = h(t) \times g(e) \times C$$

$$\text{where } h(t) = \begin{cases} 0 & t<4 \\ 1/4 & 4<t\leq 5 \\ 1 & 5<t\leq 12 \\ \exp[-0.0693\,(t-12)] & 12\leq t \end{cases} \qquad h(t) = 0.203$$

$$g(e) = 0.018 \times \exp[-0.0016\,(e-20)^2] + 0.018 \qquad g(e) = 0.0353$$

C is the exposure in WLM $\qquad C = 10$

Therefore

$$ERR = 0.203 \times 0.0353 \times 10$$
$$ERR = 0.072$$

so that

$$PC = 6.7\%.$$

EXAMPLE 15

The same as Example 14, except that the man was exposed to 10 WLM every year for 10 years, starting at the age of 20 years.

In this case, the excess relative risk for each year's exposure is given by

$$ERR = h(t) \times g(e) \times C(d)$$

and since the dose to the lung is the same in each year and all of the exposure occurred more than 11 years before the diagnosis of the lung cancer ($t \leq 12$), the only change in the ERR for each year's exposure arises from the change in the age at exposure, e.

Since

$$g(e) = 0.018 \times \exp[-0.0016(e20)^2] + 0.018$$

g(e) varies from 0.036 for age at exposure of 20 years, to 0.0338 for e of 29 years, so that the ERR varies from 0.0731 for the exposure at the age of 20 years, to 0.0686 for the exposure at the age of 29 years.

Summing the ERRs for each year's exposure from the age of 20 years to the age of 29 years gives:

ERR = 0.7148

so that

PC = 42.7%.

8. SUMMARY

The purpose of this summary is to draw on the salient points which arise from the preceding sections. The subject overall is complex and the need to understand the limitations of the methods used to calculate the probability that any cancer in an individual may have been induced by exposure to ionizing radiation at work is essential. These have not been placed in a priority order but as a sequence for those considering the subject. The reference to a section is designed to lead the reader to the section where most of that information can be assessed.

There are many causes of cancer. Ionizing radiation is one known causal agent but it is not responsible for the majority of cancers in the general population. Radiation induced cancers cannot be recognised in an individual but only inferred by an examination of the risks, which are random in nature (Sections 2 and 3).

Risk factors have been developed from epidemiological studies of exposed populations showing an increasing risk (incidence) of cancer with radiation dose (Section 4).

There are many uncertainties in the risk factors so it is preferable to use widely accepted risk models, e.g. those used by UNSCEAR, rather than unique ones within a specific country (Sections 4 and 6).

Relative risk models are preferred; however, occupational exposures which involve radon may require the use of alternative models. The models used do not apply to chronic lymphatic leukaemia and Hodgkin's disease (Section 4).

Probability of causation (PC) calculations offer the best method of systematically quantifying the probability that a particular cancer may have been induced by radiation in an individual. They are not ideal but are the only practicable method currently available (Section 5).

When there is a claim for compensation by those who have been occupationally exposed to ionizing radiation, it is very important that Member States ensure the cancer incidence and mortality registers are reliable. The background rates for cancer in any country are important for the PC calculations (Section 5).

Accepted differences in the latency of cancers may exclude certain cases (Section 6).

PC calculations should not be applied in compensation claims from radiation exposures other than those sustained during employment; for example, medical exposures should be excluded (Section 4).

Appendix I

FACTORS AFFECTING CANCER RISK

This appendix summarizes observations of the Japanese atomic bomb survivor cohort and those of various therapeutically irradiated groups with a view to determining patterns for variation in relative risk by time since exposure and evidence for curvilinearity of dose-response. The limited information on groups exposed to high LET radiation will be assessed separately Although various populations were exposed to radiation which might be thought to have a substantial high LET component, e.g. the groups of women treated with radium for treatment of benign gynecological diseases [88, 89] and cervical cancer [45], because of the cladding in which the radiation sources were administered, the tissue dose would have been predominantly from low LET emissions.

Corresponding to the main cancer type groups presented here, Appendix II gives further details of the two sets of models considered in detail in this Report, corresponding to the generalised relative risk models fitted to the Japanese atomic bomb survivor Life Span Study (LSS) 11 mortality data by the BEIR V committee [11] and the generalised relative and absolute risk models fitted to the recently published Japanese atomic bomb survivor cancer incidence dataset by the Radiation Effects Research Foundation (RERF) [36, 133] and as used by UNSCEAR [39] in population cancer risk calculations.

(a) Leukaemia, multiple myeloma and lymphomas

Various studies of therapeutic exposure have demonstrated excess incidence of (or mortality from) leukaemia associated with low LET radiation [19, 40, 48, 51, 57, 58, 59, 60, 63, 66, 71, 72, 74, 78, 80, 86, 88, 100, 103, 114, 116, 132, 136]. There have been a few studies (all involving groups given Thorotrast) in which such an excess is seen in populations exposed to high LET radiation [42, 92, 129]. In the Japanese bomb survivors[16, 36], the UK ankylosing spondylitis patients [40] and various other datasets [19, 40, 48, 63, 74, 88, 103, 114, 132] the relative risk of leukaemia falls off markedly with increasing time more than about 10 years after exposure. The opposite pattern is seen in a group of epileptics treated with Thorotrast [42], although since the bone marrow receives dose continuously after the Thorotrast injection this finding is difficult to interpret.

There is a significant correlation between mortality from multiple myeloma and radiation dose in the Japanese bomb survivor dataset for cancer mortality [16] but not for cancer incidence [36]. Cuzick [61] surveys a number of studies and finds suggestive evidence for links of multiple myeloma with medical irradiation. An excess of multiple myeloma has been observed in a group of Danish patients exposed to Thorotrast [42], in a US cohort followed up after diagnostic X rays [46], in a group of Scottish women treated for metropathia haemorrhagica [63] and in the UK ankylosing spondylitis cohort [40]. A number of therapeutically treated groups (all given low LET radiation) also display significant excesses of non-Hodgkin's lymphoma and other lymphomas [40, 78, 86, 103] although no such excess is apparent in the Japanese bomb survivors [16, 36]. It should be pointed out that the BEIR committee [11], surveying both epidemiological and animal data, does not find consistent evidence for non-Hodgkin's lymphoma being radiation-inducible.

There are non-significant indications of a decreasing relative risk for multiple myeloma mortality with time after exposure in the bomb survivors [16] but in the Scottish metropathia haemorrhagica women there were indications of an increasing trend in relative risk with time

after treatment [63]; in the UK spondylitics [40] there is a significant reduction in the relative excess of non-Hodgkin's lymphoma 25 or more years after exposure compared with the early years of follow-up (between 5 and 25 years after exposure).

The RERF [16, 35] has examined the dose-response curves for cancer in the bomb survivors and found that while for solid tumours there is little evidence for any upward curvature (convex from below) in the dose-response, for leukaemia there is quite a marked quadratic component i.e. significant upward curvature. This has been confirmed by the BEIR committee analysis of the same data [11]. The only other studies in which an analysis of the shape of the dose-response curve has been undertaken are the IRSCC patients [19], a group of women treated for benign gynecological disorders [88] and the UK spondylitics [40]. In the IRSCC study both pure linear and quadratic models (with exponential sterilisation terms) fitted the data well [19]. A linear model adequately fitted the dose-response in the UK spondylitics [40]. For all of these studies apart from the Japanese, doses were administered in a highly non-uniform fashion, so that in some bone-marrow compartments doses were clearly in the cell sterilisation range; the use of imputed average dose estimates for the purposes of a dose-response analysis would therefore be problematic. The IRSCC data was analysed using a model which utilised doses in a variety of bone-marrow compartments [19], unlike the dose-response analysis of the other two groups which used a simple average bone marrow dose [40, 88] for this reason perhaps more weight should be given to the results of the modelling of the dose-response in the cervical cancer data.

(b) Breast

A large number of studies link breast cancer with exposure to ionizing radiation. Apart from the Japanese bomb survivors [16, 38] and the UK spondylitics [40], significant radiation-related excesses of breast cancer have been manifest in various therapeutically irradiated populations [21, 30, 37, 47, 56, 69, 73, 77, 84, 85, 96, 103, 130]. Of these groups only the German ^{224}radium patients [130] were exposed to high LET radiation. There are significant reductions in relative risk 25 or more years after exposure in a group of Swedish women treated for benign breast disease [96] and there are non-significant indications of such a decrease also in a group of women treated fluoroscopically for respiratory tuberculosis [30] and in a Scandinavian group followed after treatment for cancer in childhood [103] (although treatment period and concomitant variations in treatment type (chemotherapy vs radiotherapy) may explain part of the pattern seen in this last study). There is no such variation in risk detectable in other groups [21, 37], and there is a statistically significant increase in relative risk with time after exposure up to 30 years after exposure in a group of adolescents treated for scoliosis [85] and up to 20 years after exposure in a group of women treated for Hodgkin's disease [77]. In the bomb survivors [16, 25] there is a suggestion that relative risk eventually decreases (30 or more years after exposure). The optimal model fitted by the BEIR V Committee to the DS86 data [11] incorporates log quadratic terms in time since exposure, which predicts an equivalent effect.

No suggestion of non-linearity has been found for the dose-response for breast cancer in the bomb survivors [16, 38]. In two studies of fluoroscopically irradiated women with tuberculosis [21, 30] there was no significant non-linearity in dose-response, nor was there any in the Rochester post-partum mastitis women [37] (though a diminution in risk was found at very high doses), or in the Rochester thymus irradiated children [84].

(c) Lung and respiratory system

Radiation-associated excesses of lung cancer have been documented in the bomb survivors [16, 38] and various other studies, both for exposure to low LET [40, 65, 72, 90, 94] and high LET radiation [129]. There is a significant reduction in relative risk (25 or more years after exposure) in the UK spondylitics [40]. The BEIR committee [44] analysis of underground miner cohorts (for whom the predominant exposure was to high LET radiation) demonstrated a significant reduction of relative risk with increasing time since exposure.

Analysis of the bomb survivors suggests that there is no non-linearity in the dose response [16, 38].

(d) Digestive organs

In the bomb survivors significant increases in mortality with dose have been observed for cancers of the oesophagus, stomach and colon [16], while for cancer incidence significant excesses have been seen for cancers of the stomach, colon and liver [38]. Significant excesses of cancer of the liver [42, 92, 102, 129, 138] and gallbladder [42, 102] have also been documented in a number of groups exposed to high LET radiation. Low LET radiation has been associated with excess incidence of cancers of the colon and other intestines [40, 52, 63, 89, 103], oesophagus [40, 64], rectum [45, 52, 60, 65, 104], stomach [45, 72, 87], pancreas [40, 65, 72] and miscellaneous digestive organs [49, 79]. A statistically significant increase in the relative risk of rectal cancer with increasing time up to 30 years after exposure has been observed in a group of women treated with radiotherapy for various cancers of the genital system [60] and there are non-significant indications of such a trend for this cancer also in the IRSCC cervical cancer patients [45] at least up to 20 years after exposure.

There is a significant increase in the relative risk of liver cancer up to 40 years after injection in a group of Danish epileptics treated with Thorotrast [42], although since the liver receives dose continuously after the Thorotrast injection the interpretation of this finding is problematic. There is no suggestion of any sort of variation in relative risk with time for stomach cancer up to 15 years after exposure in the IRSCC women [45] nor for colon cancer in the Scottish women treated for metropatbia haemorrhagica up to 30 years after exposure [63], nor for digestive cancers analysed as a whole in the bomb survivors [38]. There are non-significant indications for a decrease in risk of colon cancer 20 or more years after exposure in a group of women irradiated for uterine bleeding [89], as also in the Japanese bomb survivors [38], and significantly decreasing trends in the risk of oesophageal cancer up to 40 or more years after exposure have been observed in a group of fluoroscopically irradiated women [64]. A significant reduction in risk 25 or more years after exposure has been seen for colon cancer in the UK spondylitics [40].

The only information on the shape of the dose-response curve for this group of cancers comes from the bomb survivors [16, 38] where there is no strong evidence of curvilinearity (although a purely quadratic response for cancer of the colon fits the mortality data best [16]).

(e) Other solid cancers

(1) Thyroid

Excess incidence of thyroid tumours has been linked to radiation in the bomb survivors [38] and in the Marshall Islanders[75]. A very large number of studies have linked thyroid

tumours with therapeutic exposure to low LET radiation [40, 49, 62, 67, 70, 76, 82, 91, 95, 97, 99, 103, 107, 108, 118, 121, 122, 124, 125, 139] most of them relating to exposure received in childhood. A comprehensive review of the radiation-related risks of thyroid cancer has been given by Shore [127].

There are no significant variations in relative risk for thyroid cancer with increasing time after exposure in the Japanese bomb survivors [38], although there are stronger indications of reductions with time from about 25 or more years following exposure in childhood in other groups [25, 95, 103, 121, 124, 125] although an appreciable variation of risk with time up to about 30 years after exposure has not been seen in certain other groups [118] and a significant increase up to 25 years after exposure has been observed in the UK spondylitics [40].

No evidence for non-linearity in dose-response has been detected in the bomb survivors [38], nor in any other group [118, 121, 124, 125]. Related to the evidence for the essential linearity of dose-response is the observation in three studies [108, 124, 125] of the lack of any altered effectiveness when the dose is delivered in a number of fractions.

(2) Parathyroid

Hyperparathyroidism is a disease resulting from excessive secretion of parathyroid hormone, generally caused by adenoma and more rarely by hyperplasia or tumour of the parathyroid gland. Hyperparathyroidism has been linked with radiation in the Hiroshima bomb survivors [68] and a number of medically treated groups exposed to low LET radiation [43, 53, 115, 120, 134].

(3) Urinary bladder

Significant dose-related excess mortality for bladder cancer has been observed in the bomb survivors [16, 38] and in various therapeutically treated groups exposed to low LET radiation [40, 45, 60, 63, 65, 66, 89, 104, 138]. Statistically significant increasing time-trends in relative risk have been observed up to 30 years after exposure in a Swedish group treated for cervical cancer [105]; there are also indications of such an increase up to 20 years after exposure in the IRSCC dataset (which includes the Swedish cases) [45] and for an increasing trend up to 30 years after exposure in the Scottish metropathia haemorrhagica women [63]. However, at least from 20 years after exposure onwards, there is little sign of such a trend in a group of women irradiated for uterine bleeding [89] nor in the bomb survivors [16, 38]. On the whole one must conclude that there is perhaps some evidence for an increase in relative risk with time after exposure at least up to about 25 years after exposure.

(4) Skin

There is a dose-related excess incidence of skin cancer in the Japanese atomic bomb survivors [38] and also in various therapeutically irradiated groups [49, 81, 83, 103, 119, 123, 137]. A comprehensive review of radiation-related risks of skin cancer has been given by Shore [126]. There are no trends with time since exposure in the bomb survivor cohort [38] although there are strong indications that at least for those exposed in childhood, the relative risk decreases from about 25 years after exposure 24, 119]. There is no evidence of non-linearity in the Japanese bomb survivor dataset [38], and nor is there, at least on the basis of administration of very large therapeutic doses, in the Israeli tinea-capitis children [119].

(5) Brain and central nervous system

There are weak indications of a trend with dose for tumours of the brain and central nervous system in the bomb survivors [16, 38]. Associations between therapeutic irradiation and tumours of the brain and central nervous system have been observed in a number of datasets, [50, 54, 83, 86, 103, 109, 110, 111, 117] all of them exposed to low LET radiation. There is no apparent variation in excess relative risk by time after exposure in either the Israeli tinea capitis children [117] or the Swedish group receiving ^{131}iodine for diagnostic purposes [86] (the authors of this last study interpreting the time-constancy as reducing the likelihood of the excess being due to radiation).

(6) Salivary gland

Salivary gland tumours have been linked with dose received in the bomb survivors [38] and with therapeutic exposure to low LET radiation in various other studies [83, 98, 101, 103, 111, 112, 128, 139].

(7) Bone

Although no dose-related excess has been reported in the bomb survivors, various therapeutically treated groups have shown radiation-associated excesses of bone cancer for both low LET [40, 64, 79, 83, 103, 116, 135] and high LET radiation [129, 130]. The only useful information on time-trends for this cancer comes from the German ^{224}radium patients, for whom there is a clear diminution in excess relative risk from about 10 years after exposure [93]. Although increasing trends of relative risk with time up to 20 years after exposure are seen in the Late Effect Study Group of people treated for cancer in childhood [135], it is difficult to be sure that this is entirely the effect of radiation, since many of the children received chemotherapy. There is no suggestion of variation in excess risk with time after exposure in the UK spondylitics [40] or in the Scandinavian second cancer cohort [103], but the information in these studies comes from a very small number of deaths and cases.

(8) Ovary

There is a significant trend with dose for cancers of the ovary in the Japanese bomb survivors [16, 37] and in a few medically treated groups given low LET radiation [60, 89, 104, 105, 138]. A slight (but non-significant) decreasing trend with time after exposure is discernible in the bomb survivors [16] 30 or more years after exposure and a similar pattern is observed in a group of women treated for uterine bleeding [89]. However statistically significant increasing trends in relative risk up to 30 years after exposure are evident in two groups of women treated for cervical cancer [60, 105]. There is no significant curvilinearity in the dose-response in the Japanese bomb survivors [38].

(9) Uterus and vagina

Radiation related excesses of uterine cancers have been documented in various therapeutically treated groups exposed to low LET radiation [55, 65, 89, 104, 105, 131, 138], but have not been observed in the bomb survivors [16, 38]. An excess of vaginal cancers is evident in the IRSCC patients [13]. There is no discernible trend in excess risk with time after exposure up to 20 years after irradiation in a group of women treated for cervical cancer [13] or in a group of women treated for uterine bleeding up to about 30 years after exposure [89].

Appendix II

RISK MODELS

Two sets of models will be presented, corresponding to the generalised relative risk models fitted to the Japanese atomic bomb survivor Life Span Study (LSS) mortality data by the Biological Effects of Ionizing Radiations (BEIR) Committee [11], and the generalised relative risk and generalised absolute risk model fitted to the Japanese LSS incidence data by the Radiation Effects Research Foundation (RERF) [36, 38] and as used by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [39] in population cancer risk calculations.

Leukaemia models

BEIR V [11] used a linear-quadratic relative risk model obtained by fits to the Japanese LSS leukaemia mortality data (ICD9 204-207) (with <4 Sv bone marrow dose, neutron relative biological effectiveness (RBE) = 20, attained age <75). Under this model, the leukaemia mortality rate following a dose of D Sv is:

$$
\begin{array}{ll}
r_0(a, s)\,[1 + (\alpha_2 D + \alpha_3 D^2)\exp(\beta_1)] & \text{if } e \le 20,\ t \le 15 \\
r_0(a, s)\,[1 + (\alpha_2 D + \alpha_3 D^2)\exp(\beta_2)] & \text{if } e \le 20,\ 15 < t \le 25 \\
r_0(a, s)\,[1 + (\alpha_2 D + \alpha_3 D^2)] & \text{if } e \le 20,\ t > 25 \\
r_0(a, s)\,[1 + (\alpha_2 D + \alpha_3 D^2)\exp(\beta_3)] & \text{if } e > 20,\ t \le 25 \\
r_0(a, s)\,[1 + (\alpha_2 D + \alpha_3 D^2)\exp(\beta_4)] & \text{if } e > 20,\ 25 < t \le 30 \\
r_0(a, s)\,[1 + (\alpha_2 D + \alpha_3 D^2)] & \text{if } e > 20,\ t > 30
\end{array}
\qquad \text{(A-1)}
$$

where $r_0(a, s)$ is the baseline mortality rate, e = age at exposure, t = time since exposure and where $\alpha_2 = 0.243\ \text{Sv}^{-1}$, $\alpha_3 = 0.271\ \text{Sv}^{-2}$, $\beta_1 = 4.885$, $\beta_2 = 2.380$, $\beta_3 = 2.367$, $\beta_4 = 1.638$.

The RERF model [36] fitted to the leukaemia incidence data excluding everybody with more than 4 Gy kerma dose, and using migration adjusted person years, employed a (fitted) parametric model for cancer incidence at zero dose in the Japanese cohort. In contrast, the BEIR V committee [11] analysis of the leukaemia mortality data estimated stratum-specific base-line (zero dose) cancer mortality rates, so that the total observed and model-expected numbers of leukaemia deaths in each stratum were equal.

The spontaneous (zero-dose) leukaemia incidence rates in the Japanese atomic bomb survivor cohort fitted by RERF [36] are given by:

$$r_0(a, e, s) = 0.91 \exp\{-0.022(e - 25) + 3.08 \log_e(a/50) + 1.22 [\log_e(a/50)]^2\} \quad \text{if } s = \text{male}$$
$$r_0(a, e, s) = 0.45 \exp\{-0.022(e - 25) + 3.08 \log_e(a/50) + 1.22 [\log_e(a/50)]^2\} \quad \text{if } s = \text{female}$$

where e = age at exposure, a = attained age.

The radiation-induced excess leukaemia risk is given by:

$$
\begin{array}{ll}
F(D)\,\beta(t, e, s) = 0.33\,(D + 0.79D^2)\exp[-0.17\,(t - 25)] & \text{if } s = \text{male},\ e < 20 \\
F(D)\,\beta(t, e, s) = 0.48\,(D + 0.79D^2)\exp[-0.13\,(t - 25)] & \text{if } s = \text{male},\ 20 \le e < 40 \\
F(D)\,\beta(t, e, s) = 1.31\,(D + 0.79D^2)\exp[-0.07\,(t - 25)] & \text{if } s = \text{male},\ e \ge 40 \\
F(D)\,\beta(t, e, s) = 0.66\,(D + 0.79D^2)\exp[-0.07\,(t - 25)] & \text{if } s = \text{female},\ e < 20 \\
F(D)\,\beta(t, e, s) = 0.97\,(D + 0.79D^2)\exp[-0.03\,(t - 25)] & \text{if } s = \text{female},\ 20 \le e < 40 \\
F(D)\,\beta(t, e, s) = 2.64\,(D + 0.79D^2)\exp[0.03\,(t - 25)] & \text{if } s = \text{female},\ e \ge 40
\end{array}
\qquad \text{(A-2)}
$$

with the notation as above.

Solid tumours

The RERF [38] fitted to each solid tumour site a relative risk model of the following form:

$$r_0(a, s)\,[1 + \alpha_s D \exp(\beta\,(e - 25))] \qquad \text{(A-3)}$$

where α_s is the age specific linear excess relative risk per Sv, D is the dose (RBE for neutrons = 10), e is the age at exposure in years and β is the coefficient determining the modifying effect of age at exposure. Separate models were fitted for cancers of the oesophagus, stomach, colon, liver, lung, urinary bladder, breast, ovary and all other sites as a group. Parameter estimates were based on models fitted to the LSS incidence data for the period 1950-1987 [38]. The parameter estimates for the model fits to all solid cancers (as a group) are as follows:

	α_s (Sv^{-1})	β (= age-at-exposure effect)
Males	0.45	-0.026
Females	0.77	-0.026

The parameter estimates, for both RERF [38] and BEIR V [11] analyses for each solid cancer site are also given below.

Female breast cancer models

BEIR V [11] used a linear relative risk model obtained by fits to the Japanese LSS 11 female breast cancer mortality data (ICD9 174) (with <4 Sv breast dose, neutron RBE = 20, attained age <75). Under this model, the breast cancer mortality rate following a dose D (Sv) is:

$$\begin{aligned} &r_0(a, s)\,[1 + \alpha_1 D \exp(\beta_1 + \beta_2 \log_e(t/20) + \beta_3[\log_e(t/20)]^2)] && \text{if } e < 15 \\ &r_0(a, s)\,[1 + \alpha_1 D \exp(\beta_2 \log_e(t/20) + \beta_3[\log_e(t/20)]^2 + \beta_4[e-15])] && \text{if } e \geq 15 \end{aligned} \qquad \text{(A-4)}$$

with the notation used in Equation (A-1) and where:

$\alpha_1 = 1.220\ Sv^{-1}$, $\beta_1 = 1.385$, $\beta_2 = -0.104$, $\beta_3 = -2.212$, $\beta_4 = -0.0628$

The form of the model was suggested by fits to various breast cancer incidence datasets. However, it is now known that the version of the Japanese bomb survivor incidence data that the BEIR V committee used was faulty, so that this model should only be used with caution.

The model fitted by the RERF [38] to the female breast cancer incidence data (<4 Gy air kerma) using the model (B3) had the following parameter estimates.

α_s (Sv^{-1})	β (= age-at-exposure effect)
1.95	-0.079

Respiratory cancer models

BEIR V [11] used a linear relative risk model obtained by fits to the Japanese LSS 11 mortality data for the group of all respiratory and intrathoracic cancers (ICD9 160-163) (with <4 Sv lung dose, neutron RBE = 20, attained age <75). Under this model, the lung cancer mortality rate following a dose D (Sv) is:

$$\begin{array}{ll} r_0(a, s)\,[1 + \alpha_1 D \exp(\beta_1 \log_e(t/20))] & s = \text{male} \\ r_0(a, s)\,[1 + \alpha_1 D \exp(\beta_1 \log_e(t/20) + \beta_2)] & s = \text{female} \end{array} \qquad \text{(A-5)}$$

with the notation used in Equation (A-1) and where:

$\alpha_1 = 0.636\ Sv^{-1}$, $\beta_1 = -1.437$, $\beta_2 = 0.711$

The form of the model (and in particular the time trend) was based on the observed patterns of lung cancer incidence in the UK ankylosing spondylitis data [14].

The model fitted by the RERF [38] to the lung cancer (ICD9 162) incidence data (air kerma <4 Gy) using the model (B3) had the following parameter estimates.

	α_s (Sv^{-1})	β (= age-at-exposure effect)
Males	0.37	0.021
Females	1.06	0.021

Digestive cancer models

BEIR V [11] used a linear relative risk model obtained by fits to the Japanese LSS 11 mortality data for the group of "all digestive cancers" (ICD9 150-159) (with <4 Sv stomach dose, neutron RBE = 20, attained age < 75). Under this model the digestive cancer mortality rate following a dose D (Sv) is:

$$\begin{array}{ll} r_0(a, s)\,[1 + \alpha_1 D] & \text{if s = male, e} \le 25 \\ r_0(a, s)\,[1 + \alpha_1 D \exp(\beta_2(a - 25))] & \text{if s = male, } 25 < \text{e} \le 35 \\ r_0(a, s)\,[1 + \alpha_1 D \exp(10\,\beta_2)] & \text{if s = male, } 35 < \text{e} \\ r_0(a, s)\,[1 + \alpha_1 D \exp(\beta_1)] & \text{if s = female, e} \le 25 \\ r_0(a, s)\,[1 + \alpha_1 D \exp(\beta_1 + \beta_2(a - 25))] & \text{if s = female, } 25 < \text{e} \le 35 \\ r_0(a, s)\,[1 + \alpha_1 D \exp(\beta_1 + 10\,\beta_2)] & \text{if s = female, } 35 < \text{e} \end{array} \qquad \text{(A-6)}$$

with the notation used in Equation (A-1) and where:

$\alpha_1 = 0.809\ Sv^{-1}$, $\beta_1 = 0.553$, $\beta_2 = -0.198$

The RERF [38] fitted models to cancer of the oesophagus, stomach, colon, liver and bladder separately, in each case excluding records with air kerma > 4 Gy, and in each case the form of the model used is that given by (B3). The model parameter estimates are as follows:

	α_s (Sv^{-1})	β (= age-at-exposure effect)
Oesophagus		
Males	0.23	0.015
Females	1.59	0.015
Stomach		
Males	0.16	-0.035
Females	0.62	-0.035
Colon		
Males	0.54	-0.033
Females	1.00	-0.033
Liver		
Males	0.97	-0.027
Females	0.32	-0.027
Bladder		
Males	1.00	0.012
Females	1.19	0.012

Models for cancers other than leukaemia, breast, respiratory and digestive

BEIR V [11] used a linear relative risk model obtained by fits to the Japanese LSS 11 mortality data for the group "all cancers other than leukaemia, female breast, respiratory and digestive cancers" (with <4 Sv dose, neutron RBE = 20, attained age <75). Under this model, the mortality rate following a dose D (Sv) is:

$$\begin{array}{ll} r_0(a, s)\,[1 + \alpha_1 D] & \text{if } e \le 10 \\ r_0(a, s)\,[1 + \alpha_1 D \exp(\beta_1(e - 10))] & \text{if } e > 10 \end{array} \qquad \text{(A-7)}$$

with the notation used in Equation (B1) and where:

$\alpha_1 = 1.220\ Sv^{-1}$, $\beta_1 = -0.0464$

The RERF [38] fitted models to the category of "all solid cancers other than oesophagus, stomach, colon, liver, bladder, lung and breast", excluding records with air kerma >4 Gy, and the form of the model used is that given by Equation (A-3). The model parameter estimates are as follows:

	α_s (Sv^{-1})	β (= age-at-exposure effect)
Males	0.59	-0.059
Females	0.39	-0.059

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ABBREVIATIONS

BEIR	(Committee on the) Biological Effects of Ionizing Radiation
DDREF	dose and dose rate effectiveness factor
DNA	deoxyribonucleic acid
ICRP	International Commission on Radiological Protection
IRSCC	International Radiation Study of Cervical Cancer
LET	linear energy transfer
LSS	Life Span Study
NIH	National Institutes of Health
PC	probability of causation
RBE	relative biological effectiveness
RERF	Radiation Effects Research Foundation
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
WLM	working level month

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