Report of the Committee Examining Radiation Risks of Internal Emitters (CERRIE)

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Preface

In July 2001, the then Environment Minister, Michael Meacher MP, announced the establishment of a group with the remit “to consider present risk models for radiation and health that apply to exposure to radiation from internal radionuclides in the light of recent studies and to identify any further research that may be needed”. The Committee thus formed, commenced its work in December 2001 and has held 16 meetings, during which it examined evidence from radiobiology and epidemiology. In June 2003, the Committee prepared a Preliminary Report that was considered by a Workshop of invited delegates in Oxford in July 2003. This final Report has been published and sent to the Committee on Medical Aspects of Radiation in the Environment (COMARE) for its consideration. It is expected that COMARE will wish to inform Ministers of its views on the Report.

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1 Introduction

1.1 Background

1 The Committee Examining Radiation Risks of Internal Emitters (CERRIE) was established by Ministers because of concern that public perception of the risks from exposure to radiation from radionuclides deposited within the body may be at variance with official scientific advice. Over the past few decades, there have been continuing scientific and public debates on whether the radiation risk models currently used to inform UK Government policy correctly estimate the risks to human health of radiation exposures, and more recently on whether they are appropriate for internal emitters.

2 Internal emitters are radioactive substances taken into the body, mainly by ingestion and inhalation. It has been recognised for some time that the uncertainties associated with the risks of internal emitters are often significantly greater than those associated with external sources of radiation. The Department of Health has had this question under review for a number of years and has sponsored much relevant research. From a historical perspective, our knowledge of radiation and its risks has progressively increased since the discovery of radioactivity in the late 19th century. Radiation risks have remained under continued scientific scrutiny and occupational safety limits for radiation have become steadily stricter[1], due in part to the reduction in general risk tolerated by society as time has progressed. It would be imprudent to presume that this process has finished.

3 Radiation risks are estimated by the International Commission on Radiological Protection (ICRP). They are legislated for by the European Union and applied in the UK with advice from the National Radiological Protection Board (NRPB). These risks are mainly derived from the health effects resulting from the very brief external irradiation from the Hiroshima and Nagasaki atomic bombs. Critical attention has focused on whether these risks may be appropriately applied to predicting the health consequences of chronic irradiation from internal emitters. A number of epidemiological studies have also been conducted using groups exposed to internal emitters. These include underground miners and members of the public exposed to radon and its decay products; individuals with intakes of radioisotopes of radium; patients who had been injected with the radioactive contrast medium Thorotrast (containing ^{232}Th); and workers in the former Soviet Union who were exposed to high levels of plutonium (UNSCEAR, 2000; IARC, 2001). These studies have allowed some direct comparisons of risk from internal emitters with risks derived from the Japanese A-bomb survivors (eg Harrison and Muirhead, 2003).

4 Debate on the ICRP approach to radiation risks increased in 1983, following the discovery[2] of an excess of childhood leukaemias and other cancers in the village of Seascale, near Sellafield, then the world's largest commercial nuclear fuel reprocessing establishment. Following the report of the subsequent enquiry by the Black Advisory Group (1984), the Government established the Committee on Medical Aspects of Radiation in the Environment (COMARE) in 1985 to examine the matter further. The COMARE First Report (1986) concluded that the estimated radiation doses, calculated from Sellafield's recorded releases and from measured radionuclide concentrations in the

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[1] In 1934, the occupational limit for radiation was equivalent to ~1.2 mSv (millisieverts or thousandths of a sievert) per day. This was tightened in 1951 to 3 mSv per week, in 1966 to 50 mSv per year, and in 1990 to the present limit of 20 mSv per year averaged over five years (with a maximum of 50 mSv in any one year) (from Stather, 1993). Expressed in per annum terms, these are 438, 156, 50 and 20 mSv.

[2] As reported by the Yorkshire TV programme 'Windscale –The Nuclear Laundry' broadcast on 1 November 1983.

environment, were too small by a factor of about 400 to account for the increased incidence of leukaemia among the children of Seascale. The current view of COMARE (Fourth Report,1996) is that:

> "… the current best estimate of the radiation doses to the Seascale population is far too small to account for the observed numbers of cases of leukaemia and non-Hodgkin's lymphoma that have occurred in the young people of the village during the period of time studied."

5 Most environment groups and some scientists have not accepted the view that the occurrence of a pronounced leukaemia cluster adjacent to one of the world's largest sources of radioactive discharges was due to coincidence or to some other unidentified factor. In their view, a more straightforward explanation was that the ICRP risk models were incorrect, and that a re-evaluation of these models was indicated. This view was reinforced by the observation of leukaemia clusters near certain other nuclear establishments. As discussed in Chapter 2, a number of recent scientific reports indicate that ICRP dose coefficients for some internal emitters are associated with relatively large uncertainties. As a result, several CERRIE members have concluded (see paragraph 41 in Chapter 3 and paragraphs 45 to 49 in Chapter 4) that the uncertainties in Seascale internal dose estimates are sufficiently large (>2 orders of magnitude for certain radionuclides and tissues) that it would be unwise to rule out radiation as a contributory factor for the effects seen at Seascale. On the other hand, some scientists have pointed to childhood leukaemia clusters in areas remote from nuclear sites. In their view, rural–urban population mixing might be an important factor in explaining most, if not all, of these clusters whether close to, or distant from, a nuclear site. In addition, a substantial error in current radiation risk estimates would have implications for the findings of other epidemiological studies: there is little evidence from these studies (see, for example, Stevens *et al*, 1990; Darby *et al*, 1992) to support the suggestion of a gross error. An additional point made by some members was that internal exposures attributable to Sellafield discharges (and lower estimated exposures near other nuclear sites) were substantially lower than those received from naturally occurring radionuclides.

6 Another concern raised by some members was the extent of the effects caused throughout Europe by radionuclides released in the reactor accident at Chernobyl in April 1986. These members cited data for infant leukaemia occurring in a number of countries after the accident and for minisatellite mutations in the children of individuals irradiated as a result of the accident. They suggested that these studies provided strong evidence of large underestimates of risks from internal emitters. Another factor, which caused concern among environment groups and some scientists, was the matter of which issues were funded for study. These factors and differences of views, together with a reported reduction in public confidence in science-based policies (see, for example, Beck, 1992) resulted in the perception by the Government of the need for a closer examination of the radiation risks posed by exposures to radiation from internal emitters.

7 Accordingly, in 2001, the Government requested the Committee on Medical Aspects of Radiation in the Environment (COMARE) to provide up-to-date advice on the risk estimates applied to radiation arising from radioactivity within the body. Consequently, on 31 July 2001, the then Environment Minister, Rt Hon Michael Meacher MP, after consulting COMARE, announced that a working group would be set up with the following remit,

> "to consider present risk models for radiation and health that apply to exposure to radiation from internal radionuclides in the light of recent studies and to identify any further research that may be needed."

8 COMARE therefore set up a group, later known as CERRIE (the Committee Examining Radiation Risks of Internal Emitters), which held its first meeting in December 2001. Although established under the auspices of COMARE, CERRIE was independent of COMARE and of its funding departments, the Department for Environment, Food and Rural Affairs (DEFRA) and the Department of Health (DH). It is understood that, following the publication of its Report and its transmission to COMARE, the Government will seek the views of COMARE on the CERRIE Report.

9 On 20 March 2002, the Environment Minister announced the membership of CERRIE. The Committee was established to be widely representative[3], containing members with a range of views, including scientists associated with anti-nuclear groups, the nuclear industry and the NRPB. The Chairman and members of CERRIE were as follows.

Chairman

Professor Dudley Goodhead OBE
Director[4], Medical Research Council Radiation and Genome Stability Unit

Members

Mr Richard Bramhall
Low Level Radiation Campaign

Dr Chris Busby
Green Audit

Dr Roger Cox
National Radiological Protection Board

Professor Sarah Darby
University of Oxford

Dr Philip Day
University of Manchester

Dr John Harrison
National Radiological Protection Board

Dr Colin Muirhead
National Radiological Protection Board

Mr Peter Roche[5]
Greenpeace UK

Professor Jack Simmons
University of Westminster

Dr Richard Wakeford
British Nuclear Fuels plc

Professor Eric Wright
University of Dundee

10 The Secretariat of CERRIE consisted of Dr Ian Fairlie throughout, Mr Paul Dorfman (March 2002 – end), Ms Marion Hill (September 2001 – March 2003), and Dr Katherine Mondon (September 2001 – January 2002). The Chairman of COMARE, Professor Bryn Bridges, Dr Hilary Walker from DH and Dr Andrew Macpherson from DEFRA attended CERRIE meetings as observers.

1.2 Format

11 The procedural format of the CERRIE exercise was loosely modelled on a previous Consultative Exercise on Dose Assessments[6] (CEDA) carried out in 2000 by MAFF/FSA under the chairmanship of Professor Bryn Bridges, the COMARE Chairman. This involved preliminary discussions with stakeholders and a number of meetings of a CEDA steering group. This group identified key issues and prepared papers for discussion at a two-day seminar to which a wider cross-section of the scientific community and other stakeholders

[3] Current draft Government guidelines to formal scientific advisory committees require that they should take into account views that may not be represented on the committees.

[4] Professor Goodhead served as Director of the MRC Unit until his retirement on 30 September 2003.

[5] Mr Roche was an employee with Greenpeace UK until 31 March 2004. He is now an independent consultant.

[6] On radiation doses to critical groups estimated from environmental transport models.

were invited, before preparation of the CEDA final report (FSA, 2001). Because the areas of disagreement and the complexity of the issues before CERRIE were greater, committee meetings played a more important part in the CERRIE process.

12 The Chairman and Secretariat of CERRIE initially held a number of preliminary meetings with the NRPB and with the Low Level Radiation Campaign to ascertain the range of views on the Committee's remit and to determine the scope of the Committee's investigations. From these meetings, a work programme was drawn up which was agreed by the Committee. The Committee held 16 main meetings and 4 meetings of its subcommittee on epidemiology between December 2001 and June 2004. An outline of the work of the Committee and its progress was made available on the Committee's website (www.cerrie.org).

13 Much of the Committee's work consisted of evaluating the available biological and epidemiological evidence of effects of exposure to radiation. In addition, the Committee devoted considerable attention to the significant uncertainties in current models for radiation doses and risks. At an early stage, the Committee recognised that the view that risks were greatly underestimated lay at one end of a spectrum of scientific opinion. At the other end was the view that current models greatly overestimated risks from low doses of radiation. Between these two extremes existed various views about the adequacy or otherwise of current models. The Committee's approach was to devote most effort to examining the evidence for the underestimation of risks. There were a number of other topics that the Committee would have liked to have discussed but did not have the time to do so: these are noted in the Report.

14 In June 2003, the Committee published a Preliminary Report of its work for the information of, and comments by, a wider audience. In July 2003, the Committee convened a three-day Workshop at St Catherine's College, Oxford, to discuss the Preliminary Report and the Committee's findings up to that date. The Workshop was attended by approximately 80 invited delegates from around the world, including representatives from the ICRP, UNSCEAR, NRPB, international health agencies, government departments and regulatory agencies, Greenpeace, Friends of the Earth and local UK groups concerned with low level radiation matters, and international scientists holding a range of views. The Workshop was considered by the participants to have made a useful contribution to the debate on low level radiation risks. The presentations made at the Workshop are set out on the Committee's website, and a report on the Workshop together with a list of its participants is contained in Appendix B. Many of the views expressed at the Workshop or submitted to it were subsequently considered by the Committee and taken into account during the Committee's subsequent deliberations.

15 Two Committee members argued that, since CERRIE was a new kind of advice-gathering body, it should discuss scientific philosophy and scientific methods. They asserted that the science of radiation was characterised by a closed cultural attitude that made it difficult to challenge its institutional values and that its practitioners had lost sight of the classic inductive, as opposed to deductive, method of inquiry. However, most other members considered that, although these matters were interesting, they did not fall within the Committee's remit nor was the Committee constituted to have sufficient expertise in these areas.

1.3 Consensus Aim of the Committee

16 The main aim throughout the Committee's work has been to reach consensus, wherever possible, on the many issues before it. Where consensus was not possible, the Committee aimed to describe the disagreement, the reasons for it, and to identify research to clarify and possibly resolve the matter. Members expended considerable time and much effort on trying to achieve some degree of agreement on both general and specific

matters and on clarifying the remaining differences. For this reason, the Committee's lifetime was much longer than originally anticipated. Indeed, due to the considerable time spent on trying to achieve consensus, there was insufficient time to consider some relevant issues on internal emitters. The Committee examined topics in an agreed order of priority until it had to turn its full attention to completing its final Report. This meant that it was unable to discuss all issues that members had put on the list – including, for example, depleted uranium.

17 The Committee recognised that internal emitters are widely used in diagnostic and therapeutic medical practice. In such circumstances, the possible detriment is set against the medical benefit. These exposures were not considered in detail. Nevertheless, some of these exposures were of significance to the Committee because they gave information on the risk to the patient arising from particular internal exposures. Other exposures, such as the administration of Auger emitters (see Annex 2C), give rise to more general concern about the dosimetric properties of this type of radiation and therefore have been considered. The Committee agreed, however, that, in principle, its deliberations were relevant to exposures received from medical uses of internal emitters.

1.4 Dissenting Views

18 This Report was drafted by all members with assistance from the Secretariat to describe the full range of views expressed by all members of the Committee. Nevertheless, two members argued that the dissonance between the Committee's views and their own was so great that attempting to express all views within a unified narrative would misrepresent their views. These members accordingly drew up a number of drafts of a dissenting statement for possible inclusion in this Report. The Committee was initially disposed towards including a dissenting statement, following the precedent of the BEIR III report (National Research Council (NRC), 1980). Consequently, over a period of three months, protracted negotiations on these drafts took place. Unfortunately, in the view of the Committee, the drafts did not adequately identify the points of dissent from the main Report. Additionally, members were concerned that they contained factually incorrect statements and assertions of a personal nature about third parties. The Committee sought legal advice which indicated that it would be considered the publisher of the dissenting statements regardless of any disclaimer notices on their contents, and would therefore be responsible for any negligent misstatements of fact or potentially libellous statements. Individual members, on a number of occasions, offered their help to the dissenting members to rewrite their dissenting statements in a more appropriate form. These offers of help were refused.

19 At its last meeting, the Committee considered a final draft dissenting statement drawn up with the help of a member of the Secretariat. In the Committee's view, this draft retained many of the perceived defects of the earlier ones. The dissenting members refused to consider further changes to their draft and stated that the Committee had to accept their final draft or nothing at all.

20 In the end, the Committee decided not to include in its Report any of the draft versions of a dissenting statement for a number of reasons. First, the drafts did not adequately identify the reasons for the disagreement with the Committee's Report. In addition, the Committee's members, as scientists, had a professional duty not to be party to the publication of incorrect statements of fact. Furthermore, some members were reluctant to expose their employers to vicarious legal liability for their actions if the Committee were to publish the dissenting statement as it stood.

21 The dissenting members stated their wish that it be recorded that the Committee's Report did not adequately reflect their views. The dissenting members said that they would not endorse the Committee's Report.

2 Risks from Internal Emitters

This chapter is in two parts. Part 1 (the panel below) has been written to be accessible to, and understandable by, members of the public and scientists who are unfamiliar with radiation issues. Part 2 is more technical and contains additional detail for scientists familiar with radiation issues.

Part 1

Introduction

1 The Committee was requested to consider the health risks from internal radiation according to current scientific evidence. This Part of Chapter 2 explains first what is meant by internal radiation. Second, it explains how the health risks from radiation are estimated. Third, it simplifies and describes how radiation doses are estimated. Fourth, as these steps require models that contain uncertainties, the reliability of current risk estimates is discussed. These issues are addressed in more detail in Part 2.

What Are Internal Emitters?

2 Many people think of radiation in terms of X-rays, which are an external form of radiation. Another source is internal radiation, that is radiation originating inside the body from radioactive matter that has entered the body by being inhaled or ingested[1]. This can occur as a result of environmental pollution, nuclear medicine treatment and background radiation from naturally occurring radioactive atoms in the earth or air. For example, about half of the predicted risk from background radiation is currently estimated to arise from inhaling a naturally occurring radioactive gas called radon and its decay products.

3 The basic constituents of radioactive matter are called radionuclides. These are unstable and when they decay they emit various kinds of radiation including alpha particles, beta particles (ie electrons or positrons), and gamma rays. For example, ^{222}Rn[2] emits an alpha particle when it decays, ^{14}C emits a beta particle, and ^{137}Cs emits both a beta particle and a gamma ray. After the radioactive decay of a radionuclide, the remaining nucleus is itself often unstable and decays further. In some cases, long chains of radioactive decays are the result, as with the decay of ^{222}Rn. An important characteristic of radioactive materials is the rate at which they decay, either into another radioactive nuclide or into a stable (ie non-radioactive) nuclide. The simplest way in which the decay rate can be expressed is by its half-life, that is the time taken for the radioactivity of a particular radionuclide to decay to half of its initial value.

[1] Breathing in radioactive particles in air or eating food and water contaminated with radionuclides. Intakes may also occur through wounds and skin abrasions.

[2] The number before or after an element indicates the number of protons plus neutrons in its nucleus. Radionuclides can be shown as, for example, radon-222, Rn-222 or ^{222}Rn.

4 A number of radionuclides emit low energy X-rays and low energy electrons from a complex decay process: these are called Auger emitters[3]. Alpha emitters, low energy beta emitters and Auger emitters all deposit their energies close to their decay sites; therefore their locations within cells and organs are important when we come to assess their health effects.

How Are Radiation Risks Estimated?

5 Cancer risks are estimated predominantly from epidemiological studies. The primary study is the ongoing Life Span Study of the survivors of the Hiroshima and Nagasaki atomic bombings in 1945 (Preston et al, 2003). This is augmented by studies of medical and other exposures to radiation. Data from these studies are used to derive estimates of how many cancer deaths are likely to result per unit of estimated radiation 'dose'. This is explained next.

6 Although the focus of this Report is on risks, these are expressed in terms of 'dose', usually either 'equivalent dose' to an organ or 'effective dose' to the whole body. It is necessary to explain these terms. Equivalent dose and effective dose are theoretical constructs derived from the physical quantity 'absorbed dose' and from observed health effects. Because it is not practical to measure radiation or its health effects in tissue, in practice 'dose' is an estimate and not a direct measurement.

7 The physical quantity 'absorbed dose' (in grays or Gy) is defined as the average energy (in joules or J) deposited per unit mass (in kilograms or kg) of tissue from an exposure to radiation. For risk estimation, this is then weighted to allow for the estimated relative biological effectiveness (RBE) of the type of radiation compared with radiations of low linear energy transfer (low LET), such as gamma rays and X-rays (to obtain 'equivalent dose' expressed in sieverts or Sv). A second weighting is applied to allow for organ sensitivities throughout the body (to obtain 'effective dose' also expressed in Sv). See Part 2 of this chapter for an explanation of technical terms.

8 Most radiation scientists accept that external radiation may be quantified by 'dose' to an acceptable degree of accuracy. Nevertheless questions remain on the adequacy of 'dose' as an accurate measure for the radiation from internal emitters that deposit their energies in small tissue volumes. One difficulty is that 'dose' implies uniform or averaged distribution of radionuclides within organs or tissues. While this may be a reasonable assumption for some radionuclides, such as ^{137}Cs, it may not be for others whose tissue distributions are poorly known – see Part 2. Consequently, some scientists (see Makrigiorgos *et al*, 1989, 1990a, 1990b; Rao *et al*, 1983; Howell *et al*, 1991, 1993; Howell, 1992; Goddu *et al*, 1996; and Faraggi *et al*, 1998) question the use of 'dose' for radionuclides with highly localised dose distributions – that is, alpha emitters, low energy beta emitters, and Auger emitters.

9 Other scientists (see, for example, Simmons, 1992) have more fundamental objections to the use of 'dose' at low levels of radiation exposure. In such cases, since not all cells can be hit by the radiation, the averaging process is considered to be unsound. As a result, it is incorrect in their view to relate health risks to 'dose' at these levels. These scientists propose that, instead of dose, fluence (ie the number of radiation tracks per unit area of irradiated tissue) should become the fundamental quantity in radiological protection. This does, however, have its own limitations. An additional issue is that 'dose' is conventionally applied as the average over an organ or tissue or part of a tissue (kg, g or mg), although in recent years a focus of attention has

[3] Some Auger emitters occur naturally, and others are found in nuclear wastes and bomb fallout. Certain Auger emitters are important in nuclear medicine.

been on the action of radiation on cells and the DNA molecule (around a billionth of a gram). The study of radiation's distribution and effects at these small levels is termed microdosimetry, but the relationship between what may be termed 'doses', energy depositions or fluences at these microscopic levels and the adverse effects or risks to the overall tissue or person remains unclear.

10 Most scientists continue to use the parameter of 'dose', keeping in mind its many limitations for internal emitters, particularly the assumption of uniform or averaged distribution within tissue.

How Do We Quantify Radiation?

11 Quantifying radiation and its effects is not a simple matter. This is because radiation is perceived by none of our senses and requires sophisticated devices to detect it. Radiation is emitted by widely different materials and in various forms which have different effects in tissues, individuals and populations. Although the physical characteristics of radionuclides, such as their half-lives and emission energies, are known to a high degree of accuracy, this is not true of the complex sequence of physico-chemical events leading to biological changes which could give rise to health risks. These factors make it difficult to estimate the amounts and effects of low doses of external radiation simply in a unified way. These difficulties are magnified in the case of internal radiation exposures. Internal radionuclide decays have widely different energies from a few electron volts to millions of electron volts, and internal radionuclides have half-lives from millionths of a second to many millennia.

12 For these reasons, the estimation of radiation doses from internal radionuclides is necessarily complicated. The process is often only hazily understood by many scientists, and not at all by lay members of the public. So that risk factors for cancer and genetic effects can be applied to radiations of all types, external and internal, the ICRP has developed a scheme that allows the addition of doses from different sources. In simplified terms, this requires the following four steps to be performed in sequence:

a the estimation of radionuclide concentrations in each tissue (using metabolic models);

b the conversion of these concentrations to absorbed dose (using dosimetric models);

c the conversion of absorbed dose to a second concept – equivalent dose (using a conversion factor called the radiation weighting factor or w_R to take into account the different types of radiation);

d the conversion of equivalent dose to a third concept – effective dose (using another conversion factor called the tissue weighting factor or w_T to take into account the different radiosensitivities of each tissue).

13 The resulting effective dose is compared with dose limits (and constraints) set on the basis of the risks of cancer and genetic effects[4]. The ICRP makes clear that effective dose is a quantity intended for use in radiological protection and not in epidemiological studies or other investigations of human exposure. For these, absorbed doses in the organs/tissues and specific data relating to radiation types in question should be used.

[4] The ICRP cites risks for fatal cancer and includes added element for non-fatal cancers and genetic effects. Non-cancer effects from radiation, such as cardiovascular effects, are not included, as there is a paucity of epidemiological and mechanistic data upon which to base risks. See Chapter 4.

14 This complex system depends on dose via the various concepts of 'absorbed', 'equivalent' and 'effective' dose. In other areas of toxicology, eg chemical and biological contaminants, amounts of intake or concentrations in tissues are often used. The above system was developed specifically for ionising radiation. It is a valid approach to estimating radiation amounts and risks within a unified system that covers the wide variety of types and scenarios of radiation exposure. Varying degrees of uncertainty attend such estimates, which remain the subject of continuing discussion among radiation scientists. These are discussed next.

Uncertainties in Current Risk Estimates

15 The Committee gave close consideration to the issue of uncertainty. The word 'uncertainty' has a number of meanings. In the strict scientific sense of the word, uncertainty arises from the use of mathematical models. These include:

a model uncertainty, ie whether the model conceptually represents the real world correctly and whether the assumptions used to make a specific assessment approximate to a range of conditions are correct, and

b parameter uncertainty, ie whether parameter values are correct.

16 It is important to distinguish between uncertainty and variability. Variability refers to the quantitative biological differences in individual members of a population. For example, two healthy people of the same age and gender and having identical diets may exhibit substantially different rates of food transit through the colon. Variability should not be confused with the uncertainty on the central value of some parameter or dose estimate for a population.

17 Doses calculated by the above models do not result in a single value but a range of possible values, often illustrated by a bell-shaped or similar-shaped distribution curve. Current ICRP dose coefficients[5] are expressed as a single value (usually the 'most probable' value, ie the high point in the distribution curve). In many cases, the range of values can be wide. Uncertainty in these models is often defined as the ratio of the 95th to the 5th percentile values in the curve: this is the definition used in this Report. Recent studies have attempted to quantify uncertainties using probabilistic techniques, and some studies (eg Goossens *et al*, 1997; NCRP, 1997) have estimated that the uncertainties in the organ dose coefficients of some radionuclides can be very large (see section 2.7 of Part 2).

Uncertainties in External Radiation Risks

18 Because of the paucity of risk data for most radionuclides, internal radiation risks are derived from the risks for external radiation, although internal data are used where these exist, eg for radon and radium. Therefore it is first necessary to consider uncertainties in external radiation risks. The Committee's consensus was that the risk estimates for external radiation have uncertainties of about a factor of three up and down from the central figure for all cancers. This recognition stems from several recent analyses which indicate that the uncertainty in present estimates of overall fatal cancer risk from low LET radiation is about a factor of two to three higher or lower than the central accepted value (see section 2.7 of Part 2). This uncertainty arose from a number of factors, including the assumed shape of the dose–response curve, the effect of different dose rates, and questions about the main study used to derive risks, the A-bomb survivor study.

[5] Defined as the equivalent doses to organs/tissues and effective dose to the body from the ingestion or inhalation of 1 Bq of a particular radionuclide.

Uncertainties in Internal Radiation Risks

19 With internal emitters, more uncertainties need to be added to those affecting external radiation. These arise from the assumptions made in deriving doses from internal radionuclides using biokinetic and dosimetric models and from the RBEs used for internal radionuclides. A key issue is the correctness of using risks derived from external, acute, large doses of high energy gamma and neutron radiation from the A-bomb blasts to derive the risks for internal, low level, chronic exposures to alpha and beta emitters. In a general sense, the Committee was concerned that reliable estimates of uncertainties were required for the many steps and parts of steps used to estimate dose coefficients of internal emitters. A number of members were also concerned that published analyses of uncertainties in dose coefficients showed large ranges for some radionuclides. Although the Committee did not attempt to quantify uncertainties in dose coefficients, it was noted that ranges for equivalent doses to organs and tissues may vary from factors of two to three above and below the central estimate for radionuclides for which good data were available to well over a factor of ten for other radionuclides. These uncertainties are additional to those applying to risk estimates.

20 Uncertainties in risk estimates and variability both have implications for the reliability of risk estimates used in radiological protection, particularly in the regulation of practices that result in exposures to radiation.

Part 2

2.1 Introduction

1 Internal emitters are radioactive isotopes of elements (generally referred to as radionuclides) that have been incorporated into the body and thus irradiate body tissues internally. 'Internal' distinguishes this source of irradiation from external irradiation from sources outside the body. Although radiation from either source is capable of inducing cancer and other biological effects, due in each case to damage caused within living cells by the ionisation of cellular constituents (see section 2.2), there are important differences in the radiation types that can contribute to internal and external exposures. Thus, in the case of external exposures, it is those radiations that can penetrate the body that give rise to radiation doses to body tissues: electromagnetic (photon) radiations (eg X-rays and gamma rays) and neutrons. Charged particle radiations – electrons (eg beta particles) and alpha particles – penetrate to only a limited extent, depending on their energies; alpha particles hardly penetrate the outer epidermis of the skin while some beta particles may penetrate up to a centimetre or so. In the case of internal irradiation, short-range charged particle emissions may be the dominant or sole contributors to radiation dose and risk, depending on the emissions of the radionuclide concerned, and its location within tissues and cells.

2 An important characteristic of radioactive materials is the rate at which they decay, either into another radioactive nuclide or into a stable (ie non-radioactive) nuclide. The decay rate is normally expressed in terms of the nuclide's half-life, namely the time taken for the radioactivity of any given amount of the particular radionuclide to decay to half of its initial value (this time period is a constant for any particular nuclide, irrespective of the actual amount present at the start). Half-lives can range in value from less than a microsecond to more than thousands of millions of years.

3 The amount of a radioactive substance may be measured in terms either of its number of radioactive atoms (proportional to mass) or, more generally, of its activity (radioactive decay rate). For the latter, the unit of activity is the becquerel (Bq), defined as a decay rate of one nuclear event per second. For radiological protection purposes, specification of the quantity of a radioactive material in becquerels is an extremely convenient standard practice, the rate of decay being readily transformed into rate of energy production, and hence used to calculate radiation dose.

4 For all types of radiation and exposure, radiation dose is defined as the energy deposited, as a result of ionisations and excitations, per unit mass of material. This quantity is referred to as absorbed dose and has the unit of gray[6] (Gy). The probability of biological damage caused by radiation is generally expressed as a risk factor, given as additional risk of a specific outcome per gray of radiation dose[7]. It is clear from extensive experimental studies of radiation effects in animals and *in vitro* cell systems that different radiation types can generate quite different probabilities of effects per unit absorbed dose, and that these differences are related to the differing densities of ionisation characteristic of each type of radiation. The most important differences in the context of this Report are between alpha particles, beta particles/electrons of high and low energy, and gamma rays. For a given radiation dose (Gy), alpha particles, which are densely ionising, are more

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[6] 1 gray (Gy) = 1 joule per kilogram (J kg^{-1}).

[7] Expressing the risk in this way carries the underlying assumption that the risk–dose relationship is linear with no dose threshold. The validity and consequences of this are discussed in section 2.3.

effective in causing cancer than are gamma rays, which are more sparsely ionising. High energy electrons are similar in their effectiveness to high energy photons, but low energy electrons (eg Auger electrons and beta particles from tritium decay) on average create greater ionisation densities, and can cause greater damage per unit dose. These differences can be quantified experimentally and be expressed simply as ratios (referred to as relative biological effectiveness, RBE), which are measures of the relative effectiveness of each type of radiation in producing a specified level of biological response. However, there are a number of difficulties with applying this concept, which are considered in section 2.2.

5 Risk estimates (see section 2.3) for radiation-induced cancers are derived mainly from studies of the effects of external irradiation, the principal source of information being follow-up studies of the Japanese A-bomb survivors. Whilst these risk factors may be expected to apply to situations similar to those from which they were derived (acute, high dose, high dose rate, external whole-body exposure to mainly gamma rays), the factors may not necessarily apply to the very different chronic, heterogeneous, low dose rate exposures to short-range charged particles that can result from internal emitters. There are a few situations where human data allow quantitative estimation of risk from alpha-emitting radionuclides and comparisons with risks from external irradiation (section 2.3), and in these situations agreement has been found to be mostly within a factor of about three. These comparisons apply to a number of radiation-induced cancers – leukaemia, bone, liver and lung cancer. However, for a number of cancer types, including colon, stomach, bladder and breast cancer, no reliable information is available on quantitative risks from internal emitters with which to check the validity of applying risk estimates for exposure to external radiation.

6 While it is generally possible to make direct measurements of external radiation exposures, estimates of internal exposures necessarily rely on models of radionuclide behaviour within the body. Because the commonly encountered radionuclides are isotopes of a variety of chemical elements, the radionuclides differ substantially in their physiological behaviour. To take account of this, it is necessary to set up biokinetic models (see section 2.4) for each element or chemically similar group of elements. These models define the uptake, transport, and distribution of an element (and hence its radioisotopes) within the body, and retention times in different tissues, considering intakes by either inhalation or ingestion, taking account of the chemical form of the intake[8]. The purpose of these models is to allow the estimation of the amounts of each radionuclide reaching each tissue or organ of the body as the result of intake by ingestion or inhalation, and the time-course of their retention in tissues/organs. The endpoint of these calculations is the total number of radioactive decays occurring in different organs and tissues per unit intake of radioactivity.

7 The next step is to estimate absorbed radiation dose (in Gy) to body organs and tissues, which is done through the use of dosimetric models (see section 2.5). These take account of the physical characteristics (types and energies of emissions) of different radionuclides, the distribution of dose within tissues/organs and ‘cross-fire’ radiation between them.

8 In order to apply the A-bomb risk factors (from external gamma radiation) to radiation of all types, both external and internal, a common dose unit has been devised by the ICRP (1991). In this scheme, the radiation unit of harm is defined as the equivalent dose, and is measured in sieverts (Sv). For any particular type of radiation, this biologically

[8] The fractional uptake of a radionuclide may vary widely depending on its physical and chemical form. The chemical form of the intake may also influence the behaviour of radionuclides absorbed to blood; that is the initial chemical speciation may persist within the body or affect subsequent speciation. These factors are taken into account to some extent in biokinetic models (see section 2.4 and Annex 2B).

equivalent dose is calculated by multiplying the absorbed dose (ie the physical dose, measured in grays) by a scaling factor, the radiation weighting factor (w_R), to take account of differences in RBE (see above and section 2.2) of different radiation types. In practice, the w_R values defined by the ICRP for internal emitters are 20 for alpha particles and 1 for all other common internal radiation types.

9 Whilst equivalent dose may be used to estimate risk of a particular cancer type in a specific organ or tissue, it is convenient for general radiological protection purposes to be able to specify a dose limit relating to whole-body radiation exposure and the overall risk of the induction of cancer and hereditary effects (ICRP, 1991; Dunster, 2003). To achieve this end, equivalent doses to tissues from all sources (external and internal) are combined, using tissue weighting factors (w_T), numerical multipliers[9] which reflect that tissue's contribution to the overall risk of radiation-induced cancer, hereditary effects and associated health detriment (ICRP, 1991). The outcome of this calculation is referred to as the effective dose, also measured in sieverts (Sv). The effective dose takes account of all sources of radiation exposure and allows comparison with dose limits and constraints.

10 The ICRP publishes dose coefficients ($Sv\,Bq^{-1}$) for intakes of individual radionuclides (see section 2.6), giving both equivalent doses to individual organs and tissues, and effective dose (ICRP, 1989, 1993, 1994b, 1995a, 1995b, 1996). Using models, doses are generally integrated to age 70 years (50 years for children) and referred to as committed doses. Dose limits and constraints relate to committed effective dose and are set on the basis of risk estimates for radiation-induced cancer and hereditary effects (ICRP, 1991). Both equivalent dose and effective dose allow the summation of contributions from different radionuclides and external radiation.

11 The ICRP has not published information on uncertainties in dose coefficients, but it is clear that the reliability of derived doses and risks is an important factor in relation to the intended applications (see section 2.7). Uncertainties will arise at each stage of the dose calculation: in the use of biokinetic and dosimetric models; in the assumptions made to try to equate different types of radiation (through RBEs); in summing contributions from the irradiation of different tissues to give a whole-body dose (using tissue weighting factors); and deriving the total risk. Uncertainties in dose estimates will vary substantially between radionuclides, depending on their types and energies of radiation emission, their chemical form, the complexity and knowledge of their behaviour in the body, and the availability of data on which to base model parameters. There are important concerns with respect to the heterogeneity of dose delivery within tissues and cells from short-range charged particle emissions, the extent to which current models adequately represent such interactions with biological targets, and the specification of target cells at risk. Indeed, the actual concepts of absorbed dose become questionable, and sometimes meaningless, when considering interactions at the cellular and molecular levels.

12 Finally, a central concern is the question of the applicability of risk factors derived largely from the A-bomb survivors, who received a homogeneous, high dose, short (high dose rate) external exposure to mainly gamma radiation. A basic assumption is that these risk factors can be applied to heterogeneous, low dose, internal exposures to charged particles.

13 The following sections examine the methodology used to estimate risks from internal emitters. Supporting information is also given in the annexes, addressing the following specific issues: microdosimetric considerations; tritium doses and risks; Auger emitter doses and risks; and alpha emitter doses and risks.

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[9] The sum of all tissue weighting factors for the body is unity, by definition.

2.2 Relative Biological Effectiveness

14 Different types of radiation are known to vary in their effectiveness in causing cancer and hereditary effects. These differences can be related to the three-dimensional structure of ionisation tracks produced by charged particles traversing tissue volumes of interest, containing sensitive cellular targets including chromosomal DNA. The linking of biological effects to track structure is one of the central research goals in the field of microdosimetry. Most commonly used in the past to inform judgements on biological effects has been a very simple one-dimensional indicator of track structure, namely the linear energy transfer or LET. This is the quantity mostly used by the ICRP to describe radiation quality (ICRP, 1991). However, more recent calculations and simulations are beginning to approach the problem of track structure complexity and how it may be related to biological effectiveness in more detail (Cucinotta *et al*, 2000; UNSCEAR, 2000). Whilst it appears that such considerations are not yet generally applicable in any simple manner to routine dosimetry and risk assessment, the Committee was generally agreed that advances in understanding in microdosimetry would be likely to improve the scientific basis for radiation risk assessment and that this would be a beneficial development. Research in this area should be promoted.

15 The two broad categories of radiation that require consideration in the context of internal dosimetry are photons[10] and charged particles, the latter including electrons[11] and alpha particles. Photons act indirectly, as essentially all the energy transfers to irradiated tissue are produced by the passage of electrons created in photon absorption (photoelectric and pair production interactions) or scattering events (Compton interactions). Thus, photon irradiation results in the production of charged particles – electrons – which generate ionisation within the medium in the same manner as beta particles.

16 Consequently, for internal emitters as for external radiation, it is necessary only to consider the ionisation interaction resulting from charged particles within cells. Essentially, the important interactions are damage caused by direct ionisation of atoms within biologically important molecules such as DNA and indirect damage caused by free radicals (principally hydroxyl), produced by interactions with water molecules. The essential difference between the biological consequences of the interactions of electrons produced through photon absorption or by beta emission is that a beam of photons is absorbed more or less uniformly throughout an absorbing medium[12], whereas beta emission occurs from the specific locations occupied by the emitting nuclide[13]. Thus,

[10] Emitted as gamma rays or X-rays, photons have no mass and travel in straight lines with the velocity of light. As a form of radioactive emissions, photons only rarely occur unaccompanied by a charged particle emission.

[11] Beta particles emitted in radioactive decay are in fact electrons released from the atomic nucleus. Whilst beta particles/electrons may be both positive (positron) and negative (more commonly), the former if and when generated have a transient existence, suffering almost immediate annihilation, usually near the ends of their tracks, with the production of two high energy gamma photons. For conventional radiation dosimetry purposes, only (negative) electrons are considered as discrete particles. However, microdosimetric evaluation would require positrons also to be considered as particle tracks.

[12] Photon absorption conforms to probabilistic laws, with high energy photons usually travelling a large distance before interacting.

[13] Electrons and alpha particles have mass and charge and progressively lose energy by ionisation and excitation of molecules along their paths. Because alpha particles are relatively massive objects, they move relatively slowly and in essentially straight lines (ie are not appreciably deflected by most collisions) for short distances (at most 100 μm). Electrons are much less massive (by a factor of ~10^4), in general travel much faster, and are deflected at each collision. The tracks fork (as additional electrons are released by collision), and the effective range in tissue may be from a few μm to several mm, depending on the initial energy. Notwithstanding this complexity, the average behaviour of emitted electrons can in principle be accurately predicted, although in practice such predictions are now made largely by statistical calculations using so-called Monte-Carlo techniques.

differences in chemical/biological effect between gamma interactions and beta decays depend not on the nature of the ionising charged particles (electrons), but on where the interaction or decay occurs. As forms of radiation, the starting assumption is that gamma photons and beta particles of similar energy can be expected to have similar biological effectiveness. However, due account may need to be taken of the tissue/cellular location of a beta-emitting nuclide, arising as a consequence of chemical preferences. The beta emitter's location becomes progressively more important as beta energies decrease, that is, as the beta particle range decreases. Such considerations would be expected to be particularly applicable to the very low energy beta emissions from tritium, for example, and to Auger emitters (see Annexes 2B and 2C).

17 The linear energy transfer (LET) of a charged particle of given energy is the average instantaneous rate of energy loss to ionisations and excitations per unit pathlength (generally expressed as keV μm^{-1}). LET values for alpha particles from radionuclides are always substantially greater than for electrons, and these emissions are referred to, respectively, as high and low LET radiations (Bolsch, 1994). In consequence, alpha particles have far shorter track lengths than all but the lowest energy beta particles, and generate ionisation densities that can be orders of magnitude greater. However, LET is not a simple property, and for a given type of particle is a function of its kinetic energy (or, more accurately, velocity). Low energy electrons, such as tritium beta emissions and Auger electrons, have greater LET values than electrons initially emitted at high energies, although towards the end of their tracks such high energy electrons show a marked increase in LET and along their tracks they produce abundant low energy secondary electrons. Thus, all so-called low LET radiations produce microscopic regions of quite high ionisation density. Alpha particles, on the other hand, are densely ionising along the full length of their tracks, with the LET increasing as the alpha particle slows down, until it passes through a maximum (known as the Bragg peak) towards the end of the track; for example, a 5 MeV alpha particle has a range in tissue of about 37 μm and its initial LET will be about half that reached at the Bragg peak at about 5 μm from the end of its range. High LET radiation has a greater propensity to cause a concentration of damage within biological molecules; such damage to DNA, including simple and complex double-strand breaks, is more difficult to repair. It has the propensity to cause mutations and chromosomal rearrangements and hence contribute to carcinogenesis and other adverse effects of radiation.

18 Relative biological effectiveness (RBE) is defined as the ratio of the absorbed dose of the reference radiation to the absorbed dose of a test radiation which is required under similar experimental conditions to produce an identical level of biological response in a particular animal or *in vitro* cellular study (ICRU, 1986; ICRP, 2003). RBE is therefore an empirical quantity, which depends on the biological system and the conditions of the experiment. RBE is usually found to vary with dose and dose rate, frequently increasing for high LET radiation to a maximum value at low dose and dose rate because of a curvilinear response at higher acute doses of the reference low LET radiation. This value is the one used in risk estimation by the ICRP (2003), as it is assumed to be a linear region of the dose–response relationships, an essential prerequisite for comparison of a higher LET radiation with the reference low LET radiation by ICRP methodology.

19 RBE also depends on the biological endpoint taken for comparison and, apparently, in some instances on the alpha-emitting nuclide (UNSCEAR, 2000), although these may be due to differences in location and energy. The limited human data that allow estimation of alpha particle RBE values are outlined below (section 2.3). These suggest endpoint-specific values of RBE, around 10–20 for lung and liver cancer and lower values for bone cancer and leukaemia. There is good evidence from animal and *in vitro* studies of RBE values for alpha emitters of around 10 or greater compared with external low LET radiations, for cancer-related effects. Studies of bone cancer induction in dogs suggest different RBE values for this endpoint for different bone-seeking alpha-emitting radionuclides, with high

values for ^{239}Pu and low values for radium isotopes (UNSCEAR, 2000). However, these comparisons are based on average skeletal doses and the differences are more likely to be attributable to the different locations of the radionuclides in bone, with greater doses to target cells near to bone surfaces from ^{239}Pu than from $^{226/228}$Ra. Thus ^{239}Pu and related actinide isotopes concentrate at bone surfaces, while isotopes of radium or strontium, which as alkaline earth elements chemically similar to calcium, tend to be distributed more uniformly through the calcified bone matrix (ICRP, 1993; Harrison and Muirhead, 2003). Human and animal data suggest that the risk of leukaemia from alpha emitters deposited in bone is lower than calculated on the basis of ICRP models. This discrepancy may be partly attributable to the overestimation of the risk of leukaemia by the use of a radiation weighting factor (w_R) of 20 for alpha particles for this disease, but the data also suggest that biokinetic and dosimetric assumptions may lead to an overestimate of absorbed dose to target cells within red bone marrow (IARC, 2001; Harrison and Muirhead, 2003). For the naturally occurring alpha emitter ^{210}Po, studies suggest that activity retained in the skeleton is quite uniformly distributed throughout red bone marrow and therefore is likely to result in some irradiation of target cells, even if they are located mainly in regions away from bone surfaces (Naylor *et al*, 1991). Alpha emitters are considered in more detail in Annex 2D.

20 Low LET radiations show differences in RBE that reflect differences in their average ionisation density. Thus, for example, low energy beta emissions from tritium (^{3}H) decay have been shown to have RBE values of up to 2 to 3 (compared to gamma rays), for endpoints including cell killing, mutation *in vitro* and induction of chromosomal aberrations (Straume, 1993; Straume and Carsten, 1993; Harrison *et al,* 2002). (See Annex 2B.) Tritiated DNA precursors represent a special case for which apparently greater RBE values may be observed, but this may be regarded as a property of the location of the emitting nuclide (ie within DNA) rather than an inherent property of the tritium beta particle. Auger electron emissions with their very low energies, very short ranges, multiple electrons and greater ionisation densities are also a special case in which high RBE values can be observed ($\geq$10), but again as a consequence of nuclide location – ie only if the Auger emitter is bound to, or is in close proximity to, DNA (Bingham *et al*, 2000). (See Annex 2C.)

21 The ICRP uses broad judgements to smooth over many of the experimental differences in RBE by the use of generic radiation weighting factors (w_R), to which a value of 20 is assigned for all high LET alpha particle irradiation, and 1 for all low LET radiations (ICRP, 1991). It is clear that this is a broad-brush simplification for radiological protection purposes. In a rigorous scientific sense, this procedure would not be regarded as acceptable. However, as a procedure in radiological protection, this approach can be defended on the grounds of simplicity, practicality and transparency, provided of course that the operational outcome can be shown not to have been unduly affected by the simplification. For example, if the purpose of the dose estimation is for comparison with regulatory limits, and use of generic radiation weighting factors leads to estimated effective doses well below the need for intervention, it can be accepted that using scientifically more rigorous (and probably costly) calculation methods would not have affected the outcome.

22 In determining RBE values for alpha-emitting nuclides, it is important that biokinetic/dosimetric assumptions are reliable. If alpha particle emissions and target cells are heterogeneously distributed within a tissue and these distributions are inadequately represented, measured RBE values could be substantially in error. This also applies to low energy beta emissions. This is a well-recognised problem and, where possible, attempts are made to take this into account. However, as discussed above in connection with the example of alpha-emitting radionuclides deposited in bone, differences in reported RBE values may in some cases reflect inhomogeneity of radionuclide and/or target cell distribution.

23 Committee members differed in their acceptance of the ICRP scheme for representing ranges in RBE values using w_R values, with arguments for greater and lower weighting factors for alpha particles and the recognition of differences in effectiveness of different low LET radiations (for example, tritium beta emissions and Auger emitters; see below and Annex 2C). Despite these differences, the Committee was in general agreement that in critical circumstances – for example, in investigations of the possible causes of a particular type of cancer – it would be important to follow the ICRP recommendation that specific information and best available data should be used, including the most appropriate treatment of RBE. It is not clear that this recommendation is universally observed.

2.3 Risk Estimates

24 Risk estimates for radiation-induced cancers are largely derived from studies of the effects of external radiation, the principal source of information being long-term studies of those who survived the immediate effects of the atomic weapons' explosions at Hiroshima and Nagasaki, in 1945 (the so-called Japanese A-bomb survivors). Thus, the risk of developing or dying from each observed type of cancer has been related to the estimated (external) radiation dose received at the time of the explosion, and for a short time thereafter from gamma radiation from environmentally deposited radionuclides. Clearly, there must be uncertainties in the radiation doses estimated for the A-bomb survivors, which carries forward as a component of the uncertainties for the various risk factors. This issue is considered below. However, an additional complication is that the risk estimates derived for the A-bomb survivors may be in error because they did not include contributions to radiation doses from internal radionuclide exposures. If this were the case, the implication would be that the A-bomb follow-up studies may overestimate the risks of exposure to external radiation.

25 A central concern, expressed by several members of the Committee, is whether the risk factors, derived largely from the A-bomb survivors, are reliable and can be applied generally. Firstly, although the exposed individuals undoubtedly received a short, homogeneous, moderate or high external dose of gamma radiation at a high dose rate, the risk factors derived from this exposure are currently applied in all situations including those at the opposite extreme in almost all respects: namely a heterogeneous, low dose exposure to charged particles at a low dose rate over a long period of time. The assumption that this extrapolation can be made quantitatively has some support from experimental data from *in vitro* and animal studies, as well as from epidemiological data on, for example, lung cancer risks in the A-bomb survivors and from occupational and residential radon exposures (see below and Annex 2D). However, it introduces an uncertainty that may affect risk estimates in either direction.

26 Additionally, there are concerns, expressed by several members of the Committee, both as to whether the cancer outcomes within the group of A-bomb survivors can realistically be regarded as representative of human populations generally, and whether the control groups used for the A-bomb studies are appropriate. It is argued, for example, that the survivors of the Hiroshima and Nagasaki bombings probably differed from their controls in many important factors, and not merely (as would be a necessary requirement for a reliable control) in the fact of their having received a momentary pulse of high level radiation. These Committee members argue that other major differences may well have existed: short-term death rates, and/or the potential for survival, of people traumatised or injured by the bombings, differences in medical and other supporting infrastructures (particularly in the immediate aftermath), population movement, environmental contamination (both radioactive and non-radioactive), absence of information for the five years before the study cohort was defined, and so on. Analyses of this topic have been conducted, for example, by Stewart and Kneale (2000) and Little MP (2002).

27 Whilst several members of the Committee think that the results of the A-bomb survivor studies provide a reasonable basis for risk estimates for general radiological protection purposes, including assessment of exposures to internal emitters, a similar number of members feel that the general application of these risk estimates is unreasonable. The remaining few members think that the risk estimates from A-bomb studies can be applied only with great caution and a clear understanding of the uncertainties.

28 There is no disagreement that predictions based on these studies should be, and continue to be, scientifically tested by reference to as wide a range of human and animal studies as possible, and that apparent discrepancies should be objectively assessed and not dismissed as anomalies. Even assuming acceptance of the current risk factors, it is important that the uncertainties in these factors are fully assessed and appreciated. Again, these uncertainties probably affect risk estimates in either or both directions, and more research is needed in this area.

29 On the basis of A-bomb mortality data, the dose–response relationship for solid cancers is consistent with linearity over a dose range up to 3 Gy with a statistically significant increase in response down to doses around 100 mGy (UNSCEAR, 2000; Preston *et al*, 2003). The corresponding data on solid cancer incidence indicate that any dose threshold (ie below which risks are not increased) would not exceed 60 mGy (Pierce and Preston, 2000). Separate studies of cancers in children exposed *in utero* to X-rays during diagnostic radiography, such as the Oxford Survey of Childhood Cancers (Bithell and Stewart, 1975), have shown statistically significant increases in childhood leukaemia and (less certainly) in solid cancers at doses of the order of 10 mGy, with risk per unit dose estimated to be compatible with that obtained from the A-bomb survivor studies, although there are large uncertainties (Wakeford and Little, 2003). In applying the risk estimates derived from the A-bomb survivor data to cancer risks at low doses and dose rates, the ICRP (1991) applies a dose and dose rate effectiveness factor (DDREF) of two. This assumption that risks per unit dose are lower at lower doses and dose rates is based on animal and *in vitro* data showing curvilinear dose–response relationships for exposure to acute low LET radiation with DDREF values in the range from two to ten. (See also the discussion of RBE in paragraphs 18 *et seq* above.) No DDREF is applied when considering risks from high LET radiation. The A-bomb survivor data are not inconsistent with a DDREF of two; indeed, the shape of the dose–response for leukaemia supports such a value (UNSCEAR, 2000). However, the data on solid cancers for the A-bomb survivors are also consistent with a linear dose–response with no DDREF (UNSCEAR, 2000; Preston *et al*, 2003). While some Committee members considered that the use of a DDREF of two for low LET radiation was the most appropriate interpretation of available data, other opinions ranged from the view that no DDREF should be applied to the view that a DDREF of two will result in the overestimation of risks at low doses.

30 Having applied a DDREF of two, the ICRP assumes a linear relationship between dose and risk at low doses. It is the consensus among radiological protection scientists that this is the best approach on current evidence (Preston, 2003). However, Committee members differed in their acceptance of this assumption for radiological protection purposes. One argument is that the relationship may be biphasic, ie at very low doses the risk may increase more rapidly than expected for a simple linear relationship, then decrease before increasing steadily at an intermediate rate. Another view is that, since at doses of a few tens of mGy and below not all accessible cells are actually hit, the concept of ‘average dose’ becomes progressively less meaningful and derivation of a relationship with risk should not be attempted. A third view is that there is no direct evidence for a linear dose–risk relationship for cancer at low doses, and that recovery or adaptation may lead to a threshold effect. Various possible dose–response relationships are represented in Figure 2.1 below. The assumption of a linear no-threshold response is certainly convenient and is not inconsistent with current observations, but as important consequences follow from the assumption it is important that this issue is addressed by further research.

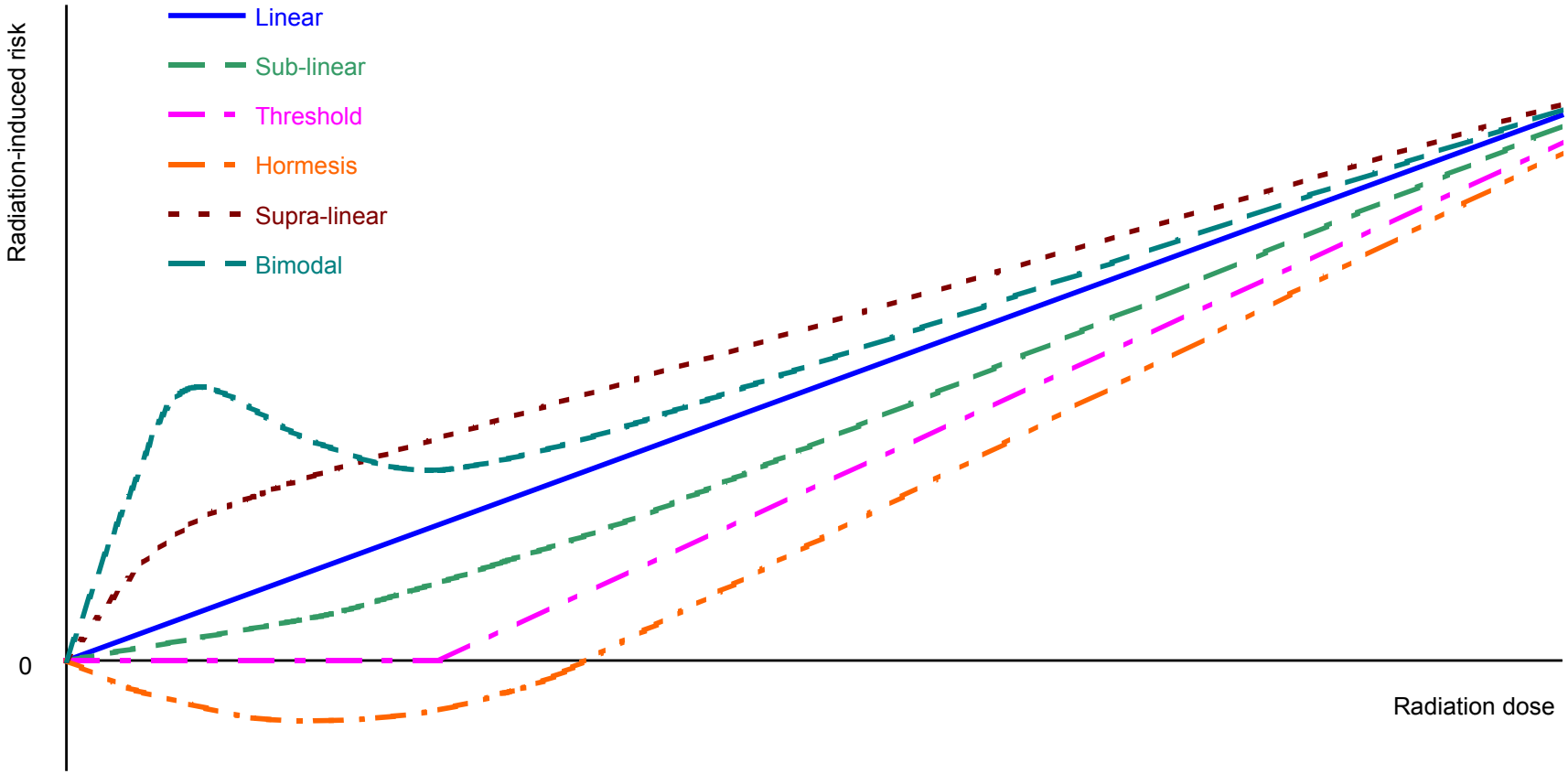

Figure 2.1 Possible dose–response curves describing the excess risk of stochastic health effects at low doses of radiation

31 In relation to the application of external risk factors to internal exposure to alpha particle irradiation, a number of human studies (UNSCEAR, 2000; IARC, 2001) provide information that has been used by the ICRP (1991) and others to estimate risks of liver, bone and lung cancer:

a liver cancer – patients given colloidal thorium dioxide (^{232}Th, an alpha emitter) as a contrast medium for diagnostic radiology;

b bone cancer – occupational exposure of radium dial painters to ^{226}Ra and ^{228}Ra, patients given ^{224}Ra for medical conditions;

c lung cancer – occupational exposure of uranium miners to ^{222}Rn and daughters, with consistent data from studies of residential exposure.

32 An excess of leukaemia has been reported in Thorotrast-treated patients[14], and quantitative estimates of ^{239}Pu-induced lung cancer have been derived for Russian workers at the Mayak nuclear site (IARC, 2001; Harrison and Muirhead, 2003). Comparisons can be made between the risk estimates for radiation-induced cancer derived for these radionuclide exposures, and those derived for the Japanese A-bomb survivors (Harrison and Muirhead, 2003). On the assumption of an alpha RBE of 20, the incidence of liver cancer in Thorotrast patients is, within the inherent range of uncertainty, consistent with that in the A-bomb survivors. However, comparison of leukaemia incidence in the two population groups can only be made consistent by reducing the applied ^{232}Th alpha RBE to around 1–2. Thus, alpha irradiation of bone marrow appears to be less effective in causing leukaemia than would be predicted on the basis of standard ICRP assumptions; animal data provide some support for a low alpha RBE for leukaemia induction. Estimates of lung cancer risk based directly on data for miners exposed to ^{222}Rn and its short-lived alpha-emitting progeny are within a factor of about 3 below estimates obtained using the ICRP respiratory tract model, an alpha RBE of 20 and risk estimates based on the A-bomb survivor studies. Similarly, approximate risk estimates have been derived for ^{239}Pu-induced lung cancer (see Annex 2D).

33 Overall, these comparisons show reasonable consistency between estimates of radiation risk from internal emitters and external radiation, for the cancer endpoints for which information is available. However, uncertainties in the dose estimates for internal emitters should be borne in mind (Harrison and Muirhead, 2003). For Thorotrast, an important consideration is the heterogeneity of distribution of particles in liver and bone marrow, resulting from their long-term retention in phagocytic cells and increasing particle agglomeration with time after administration. This results in a heterogeneous pattern of dose delivery to cells, with high local doses likely to result in cell killing. In consequence, the biologically significant dose to target cells may be overestimated.

34 In addition to the above human studies, data comparing the effects of different radionuclides and external radiation are available from a variety of studies using animals and cells *in vitro*. Such studies provide information on RBE and dose–response relationships as well as mechanisms of radiation effects. Although the absence of observable heritable effects in the children of irradiated A-bomb survivors is broadly informative, animal data provide the only direct estimates of risks of radiation-induced hereditary effects. On the specific issue of risks from local 'hot' particle alpha irradiation of tissues, animal studies of chromosomal aberrations and cancer in liver after 'hot' particle irradiation suggest that effects can be related to average tissue dose (Brooks *et al*, 1974, 1983; Barcellos-Hoff and Brooks, 2001; see Annex 2D).

[14] 'Thorotrast' is an imaging agent containing thorium dioxide, used clinically in the 1930s and 1940s. It is an insoluble material consisting of relatively large particles. The thorium content is natural thorium, ^{232}Th, which is an alpha emitter, and its decay chain includes six additional alpha emitters.

2.4 Biokinetic Models

35 The ICRP biokinetic models[15] consider intakes by ingestion and inhalation by adults and children (ICRP, 1989, 1993, 1994b, 1995a, 1995b, 1996). Doses to the fetus following maternal intakes are also calculated (ICRP, 2001). Models of the alimentary and respiratory tracts are used to define the movement of radionuclides within these systems, resulting in absorption to blood and/or loss from the body (ICRP, 1979; 1994a). Movement of ingested radionuclides through the gastrointestinal tract is quantified by transit times between the stomach, small intestine and regions of the large intestine, with absorption to blood occurring in the small intestine. The proportion assumed to be absorbed to blood depends on the chemical properties of the element and, in some cases, on the chemical form ingested. The proportion may range from complete absorption, eg for iodine or caesium, to less than 0.1%, eg for plutonium (ICRP, 1989). In the case of plutonium, several absorption factors may be used, depending on the solubility class of the compounds in question. Inhaled particles containing radionuclides are assumed to deposit in the nose, the bronchial and bronchiolar airways of the lung, and the alveolar respiratory region, with the deposition in the different regions being dependent on particle size (ICRP, 1994a). Removal from the lungs occurs by dissolution and absorption to blood and the competing process of escalation of particles from the lung to the throat followed by their entry into the alimentary tract. The proportions absorbed to blood or escalated depend on the solubility of the material and on the radioactive half-life of the radionuclide.

36 The behaviour of radionuclides absorbed to blood is described by element-specific systemic models (ICRP, 1989, 1993, 1994b, 1995a, 1995b, 1996). These range in complexity from very simple models that assume uniform whole-body distribution (eg hydrogen and caesium) to multi-compartment recycling models that take account of movement within and between body organs and tissues (eg strontium, lead, uranium and plutonium). For the simple example of hydrogen (tritium, ^{3}H), intakes as tritiated water (HTO) or organically bound tritium (OBT) are considered by the ICRP, with uniform whole-body retention of components representing HTO and OBT (half-times of retention of 10 days and 40 days, respectively, in adults; shorter in children). (See Annex 2B.) The most complex models are those developed for the bone-seeking alkaline earth and actinide elements (including strontium, radium, thorium and plutonium). These models represent the behaviour of the elements within bone, taking account of initial deposition on bone surfaces, exchange with or burial within bone mineral, and movement to bone marrow. The physiological realism of these models includes movement between organs and tissues via the circulation. In addition, the recycling models were designed to fit excretion data and can be used for bioassay interpretation. Simpler models for other elements are less suitable for this purpose.

37 The reliability of biokinetic models depends on the quality of the data on which they are based, including the availability of human data (see section 2.6). For a number of elements and their radioisotopes, there are few or no human data for use in model development or validation, and reliance is placed on the results of animal experiments and chemical analogues. Apart from the limitations imposed by the extrapolation of animal

[15] In this Report, a 'model' is taken to be a quantitative mathematical representation of a physical or biological system, and such models are used to predict outcomes in relation to the uptake and distribution of radioactive materials in humans, and the consequent internal irradiation of tissues. The mathematical functions within such models are constrained by numerical parameters, which are part of the model and which are assigned specific values in order to carry out calculations using the model. Biokinetic models seek to represent the behaviour of defined elements and their radioisotopes within a system of one or more compartments intended to represent the essential physiology of the system in question. The reliability of such models depends on the appropriateness both of their concept (physical structures and mathematical functions) and of the numerical values assigned to the parameters.

data to humans, there is a potentially important deficit in knowledge of biological variability in population groups, occurring between normal healthy adults and children, between different racial and ethnic groups, and resulting from differences in health status between otherwise similar individual members of a population group.

38 The ICRP model of the respiratory tract considers the escalation of particles out of the lung and the slow movement of particles to regional lymph nodes but does not consider entry of intact particles into the circulation (ICRP, 1994a). It is assumed that radionuclides reaching blood, directly from the respiratory tract or indirectly via the alimentary tract, do so entirely in soluble form following particle dissolution. The Committee considered the possibility that direct uptake of inhaled particles into blood may present a significant route of exposure, neglected by the ICRP, particularly in the context of the possible transfer of particles to the fetus. Evidence was presented that some entry of highly insoluble particles into blood may occur over long time periods, involving their release from lymph nodes and movement along lymphatic vessels. However, the likely fate of such particles would be their rapid removal from blood by specialised cells in the liver, spleen and bone marrow. The placenta presents an additional barrier to transfer to the fetus. However, a minority of members maintained the view that transfer of particles containing radionuclides to the fetus may be important in leukaemogenesis *in utero.*

2.5 Dosimetric Models

39 Biokinetic models for individual elements and their radioisotopes are used to calculate the total number of radioactive decays (transformations) occurring within specific tissues, organs or body regions (source regions) during a given period of time (usually to age 70 years; see section 2.6). Dosimetric models are used to calculate the deposition of energy in all important organs/tissues (targets) from each source region, taking account of the energies and yields of all emissions (Eckerman, 1994). This is done using 'mathematical phantoms' that describe geometric relationship between different tissues and organs. Phantoms have been developed for adults, children of different ages, and the pregnant woman and fetus for each trimester of pregnancy (ICRP, 2001). Absorbed dose in gray can then be calculated, knowing the number of decays occurring in source regions and energy deposition in target regions.

40 Cross-fire radiation between source and target tissues is important for penetrating photon radiation. For 'non-penetrating' radiation, including alpha and beta particles, energy will in most cases be largely deposited in the tissue in which the radionuclide is deposited. However, source and target considerations are taken into account for alpha and electron emissions in a number of important cases. These include:

a doses to target cells in the walls of the bronchiolar airways from radionuclides in the mucus layer within the airway;

b doses to target regions in the gut from radionuclides in the lumen;

c doses to cells adjacent to inner bone surfaces (taken to be a 10 μm layer) and all red bone marrow from radionuclides on bone surfaces and within bone mineral;

d cross-fire irradiation between fetal tissues (electron emissions).

41 For all dose calculations, radionuclides are assumed to be uniformly distributed throughout source regions, although these can be whole organs (eg liver) or a thin layer within a tissue (eg bone surfaces). Similarly, target cells are assumed to be uniformly distributed throughout target regions that vary in size from whole organs to layers of cells.

42 Committee members expressed varying degrees of dissatisfaction with the ICRP dosimetric models. For longer-range radiations, the consensus was that the dosimetric models are generally satisfactory. However, the spatial resolution of biokinetic and dosimetric models may not be high enough to take account of the heterogeneous distribution of very short-range charged particle emissions (eg alpha emitters, low energy beta emitters such as tritium, and Auger emitters) in relation to target cells and sub-cellular structures, and most importantly those ionisation events which may specifically affect the cell nucleus and its DNA. This problem may, in specific instances, be a major underlying cause of uncertainty, and possibly error, in dose calculations for internal emitters. Members differed in the extent of the perceived problem but agreed that this area should be identified as one in which more research effort is needed. A thorough understanding of microdosimetry would appear to be an essential pre-requisite. The Committee recommends that steps be taken to fund and support appropriate research.

2.6 ICRP Dose Coefficients

43 To enable the interpretation of absorbed dose in different tissues in terms of the risk of cancer and hereditary effects, the ICRP (1991) uses the concept of equivalent dose. Derivation of equivalent dose uses radiation weighting factors (w_R) to take account of the RBE of different radiation types in causing malignancy or genetic damage[16]. Thus, absorbed doses (Gy in joules kg^{-1}) to the various organs/tissues, obtained using biokinetic and dosimetric models as described above, are multiplied by a w_R of 20 for alpha irradiation and 1 for electron and gamma radiations to give equivalent doses (in sievert (Sv) dose units[17]). Tissue doses are commonly integrated over a 50-year period for adults and to age 70 years for children and the resulting values are referred to as committed equivalent doses.

44 The ICRP (1991) uses the additional concept of effective dose, which in effect applies the concept of a whole-body dose in the context of internal emitters. To estimate the whole-body effective dose, tissue weighting factors (w_T) are assigned to various tissues and organs. These weight their respective contribution to the total incidence of radiation-induced fatal cancer and hereditary effects, with adjustments for the incidence of non-fatal cancer and years of life lost. For example, w_T values for liver and lung are 0.05 and 0.12, respectively. Committed effective dose is the sum of all committed equivalent doses multiplied by the appropriate tissue weighting factors.

45 For simplicity in dose estimation, the ICRP publishes tables of dose coefficients, giving values of committed equivalent dose and committed effective dose per unit intake of specified radionuclides by ingestion or inhalation (units: Sv Bq^{-1}). Current ICRP risk estimates for population exposure are 0.05 Sv^{-1} for fatal cancer and 0.07 Sv^{-1} for total aggregated detriment, including hereditary effects, and making allowance for non-fatal cancer. The ICRP has published dose coefficients for radionuclide intakes by adults and children of different ages, and for irradiation of the fetus following radionuclide intakes by the mother (ICRP, 1989, 1993, 1994b, 1995a, 1995b, 1996, 2001).

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[16] At first sight, the radiation weighting factor and RBE would appear to be the same quantity, but there is an important difference. RBEs are derived experimentally, generally cover a range of values for a particular radiation type and different measured endpoints (see section 2.2), and thus have empirical authenticity relating to the circumstances of their measurement. The radiation weighting factor is a subjectively-derived generic value, that is, in the judgement of the ICRP, the most appropriate generic value for a given radiation type taking account of the observed range of RBEs.

[17] Formally, both the gray and the sievert appear to have the same physical dimensions, J kg^{-1}, although they are clearly distinct quantities and should not be used interchangeably. The sievert is not a physical unit.

46 ICRP w_R and w_T values are defined for the purpose of calculating equivalent dose and effective dose, respectively, and do not take full account of known differences in RBE and tissue radiosensitivity. Thus, as discussed above, the use of just two w_R values does not reflect observed differences in alpha particle RBE values and between different low LET radiations. Similarly, although specific risk estimates are available for each of the tissues given w_T values, in assigning these values they were simply grouped into four categories with values of 0.01, 0.05, 0.12 or 0.2. The dose coefficients for effective dose (ie committed effective dose per unit intake) have been doubly weighted[18], and are intended primarily for planning purposes in situations where doses are likely to be substantially lower than dose limits. The ICRP (1991) stated that:

> "For the estimation of the likely consequences of an exposure of a known population, it will sometimes be better to use absorbed dose and specific data relating to the relative biological effectiveness of the radiations concerned and the probability coefficients relating to the exposed population."

47 The Committee agreed that it is important that these recommendations be properly understood, and applied to situations where doses approach dose limits, in retrospective dose assessments, and in the interpretation of epidemiological data. In many such circumstances consideration of uncertainties would also be important. In particular, it needs to be appreciated that effective doses cannot be used in the evaluation of the potential causes of specific cancers, for reasons discussed below.

48 Committed effective dose can be seen to provide a convenient whole-body parameter for use to ensure compliance with dose limits and constraints, which are based on judgements regarding tolerable levels of risk. However, use of effective dose does not reveal any information about the way in which the dose is made up, and indeed can conceal very different contributions to dose and risk from the irradiation of individual organs or tissues, and in the time-course of dose delivery. For example, consider groups of individuals each exposed to a committed effective dose of 20 mSv. The doses to each group may comprise an almost infinite variety of components a group might have received. Possible variations include:

a a uniform whole-body dose of 20 mGy from external low LET radiation;

b a committed equivalent dose of around 400 mSv to the thyroid (with very low doses to other tissues) after ingestion of ^{131}I (thyroid w_T = 0.05);

c committed equivalent doses largely to liver (~140 mSv) and skeletal tissues (bone surface ~670 mSv; red bone marrow ~30 mSv) after ingestion of ^{239}Pu (absorbed doses of ~7 mGy to liver, 34 mGy to bone surfaces and 2 mGy to red bone marrow); and

d any other equivalent combination.

49 Thus, whilst a dose of 20 mSv implies an associated risk of 0.02 x 5 = 0.1 fatal cancers per 100 population, in case (a) these should encompass the whole range of cancer possibilities, case (b) would be expected to be restricted to thyroid cancers, and case (c) would be expected as an appropriate mix of leukaemia, liver and bone cancers. Furthermore, whilst both the external dose and the internal dose from ^{131}I would be delivered within the year following intake, the dose from ^{239}Pu, because of its long half-life and long retention times in tissues, would be delivered over 50 years, with only about 5% in the first year. Such differences suggest that circumspection is required in the use of

[18] That is, the calculated dose (in Gy) has been multiplied by two factors, w_R and w_T, both of which incorporate a risk component for the outcome in question (cancer). The quantities called 'equivalent dose' and 'effective dose' are not physical radiation doses.

effective dose when applied to different radionuclides singly or in combination, as the interpretation of a single, whole-body quantity is bound to be ambiguous.

50 The two[19] Committee members who had been involved in formulating the alternative methodology given in the 2003 Recommendations of the European Committee on Radiation Risk (ECRR, 2003) outlined their approach. The intention was to remedy perceived deficiencies in the ICRP methodology in a simple and pragmatic manner by introducing additional weighting factors, w_J as a biophysical hazard factor, and w_K as an isotope biochemical hazard factor. An example given in the ECRR report is that ^{90}Sr binds to chromosomes and also has sequential beta emissions, from ^{90}Sr and subsequent decay of ^{90}Y (see Chapter 3), attracting a w_J of 10 and w_K of 30, a total enhancement of 300. However, other members pointed to a lack of evidence for risks from ^{90}Sr that were orders of magnitude greater than expected. They also noted that w_J and w_K values given in the ECRR report (ECRR, 2003) for a range of radionuclides were not accompanied by any evidence or references. The majority of members were not persuaded of the scientific merit or validity of the ECRR (2003) approach on this matter.

2.7 Uncertainties

51 Uncertainties in the estimation of equivalent and effective doses arise at a number of stages in the calculations, namely:

a in biokinetic and dosimetric models – model structure, and parameter values, variability in the chemical form (and hence absorption to blood) of an ingested or inhaled radionuclide, physiological variability in humans;

b in estimation of equivalent dose – values of RBEs and their applicability to cancer in humans, choice of radiation weighting factors; and

c in estimation of effective dose – values of tissue weighting factors (arising from uncertainties in estimating risk factors for external dose).

52 In addition, uncertainties in risk assessment will arise from uncertainty in estimates of external dose and of environmental radionuclide exposures. Thus, as a precursor to the application of biokinetic models, it may also be necessary to consider uncertainties in the environmental and food chain transfer of radionuclides and their intakes by ingestion and inhalation. Whilst this topic may be deemed outside the Committee's remit, estimation of the risk of harm from internal emitters in any particular real situation, prospective or retrospective, must necessarily be based on a quantitative estimate of nuclide exposure. Thus, whilst the methodology for estimating risk from internal emitters does not encompass consideration of environmental models of exposure, uncertainties in the input data for the actual calculation of risks must be considered as a component of the overall uncertainty in the risk derived from the dose calculation.

53 It is important to distinguish between uncertainty and variability. Uncertainty refers to the level of confidence that can be placed in a given parameter value or prediction of a model or estimate of the central value of dose for a population. Variability (strictly, biological variability) refers to quantitative differences between different members of the population in question. For example, two healthy people of the same age and gender and having identical diets may exhibit substantially different rates of transit of material through the colon. However, variability will be an important source of uncertainty in the estimate of a central value when the estimate is based on a few, highly variable observations.

[19] Dr C Busby and Mr R Bramhall.

54 In addition to uncertainties in model structure and in numerical values for model parameter values, there are conceptual uncertainties associated with a number of stages in the calculation of dose coefficients. Conceptual uncertainties include:

a the use of mathematical models to represent radionuclide biokinetics – these models may either be too simple to be realistic or too complex to be parameterised;

b the geometric relationship between sources and targets – these relationships are likely to show biological variability and there are uncertainties concerning the location of sources and targets within tissues;

c the universal use of absorbed dose as the indicator of harm – at microdosimetric levels, use of ionisation density, flux or fluence may be more appropriate;

d the reliance on simple factors (RBE/w_R) to take account of differences in the biological effects of differing types of radiation;

e the concept of a whole-body dose in the context of internal emitters, and the consequent requirement for the concept of tissue weighting factors; and

f the assumption of linearity of dose responses and hence additivity of components of risk.

55 Uncertainties in biokinetic model assumptions principally arise from the quality and uncertain applicability of the experimental data on which they are based and on the complexity of behaviour of the radionuclide (Leggett, 2001, 2003). In some cases, good human data are available and uncertainties are small (eg tritium as HTO in adults). In other cases, assumptions rely on animal data and/or chemical analogy between elements, and uncertainties can be substantially greater (eg doses to the bone marrow in children and the fetus from ^{239}Pu). Levels of knowledge vary widely, with good and detailed information on nutrient and essential elements (eg carbon, hydrogen, sulphur, phosphorus, iron, iodine, copper and zinc), major toxic elements (eg lead, cadmium and arsenic), and major radionuclides (eg ^{90}Sr, ^{137}Cs, ^{238}U and ^{239}Pu), but information is much less detailed for many minor elements (eg cobalt, manganese and selenium) and radionuclides (eg ^{60}Co and ^{99}Tc). A related feature of some of the more important radionuclide elements is that they do not occur naturally, and knowledge of their chemistry may be more limited than for biologically essential, trace or toxic elements. Whilst this does not set the artificial nuclides apart in relation to the nature of their emissions of radiation, it may set some of them apart by reason of current levels of understanding of their individual chemistry.

56 A primary source of uncertainty is the chemical form of the radionuclide inhaled or ingested (Harrison *et al*, 2001). The ICRP dose coefficients are based on generic assumptions regarding inhaled particle sizes and the solubility of radionuclides in the respiratory and alimentary tracts. Specific information may be available on the chemical form of the intake. It would be inappropriate, for example, to use the generic model for ingested ^{137}Cs if the intake was known to be in an insoluble particulate form. Default assumptions regarding solubility in the respiratory tract can and should be substituted by specific information when the intake is of known chemical form. Further research is needed to extend the information base available in this area.

57 A further source of uncertainty in biokinetic models is the design of the models themselves and the adequacy of their representation of the physiological and biochemical processes determining the distribution and retention of radionuclides. An example might be uncertainties concerning the differences between bone-seeking, alpha-emitting radionuclides in their distribution on different bone surfaces (resting, growing, resorbing), their rates of incorporation into bone mineral, and propensity for uptake by macrophages

in red bone marrow – determining the risks of bone cancer and leukaemia. A fundamental problem is that whilst physiological systems are generally highly complex, the mathematical representations of them (ie the models) need to be simple enough to be constructed and parameter values set on the basis of available experimental data. Additionally (and perhaps ideally), independent experimental data should be available to validate the model once set up. Shortage of detailed experimental data, especially from humans, is a major factor in the uncertainties associated with biokinetic models.

58 Simplifying assumptions made in the calculation of dose that may not always be realistic include the homogeneous distribution of both radionuclides and deposited energy within source regions and the homogeneous distribution of target cells within target regions. For example, the distribution of Thorotrast, and dose from ^{232}Th alpha particles in liver, becomes increasingly heterogeneous with time after deposition (NCRP, 2001). Although marrow adjacent to (endosteal) bone surfaces is treated as a uniform target for bone cancer induction, evidence indicates that the cells present in this layer will differ markedly in different regions. Uncertainties are also introduced by the assumptions made in the formulation of mathematical phantoms. In some cases, it may be necessary to consider heterogeneity of energy deposition within cells – for example, for tritium bound to DNA or for Auger emitters that may concentrate in cell nuclei (see Annexes 2B and 2C).

59 Questions arise regarding the use of dose as an indicator of harm, and hence as a measure of risk from internal emitters. This applies particularly to high LET radiation (alpha particles), but may also apply to emitters of low energy electrons (eg beta particles from tritium or Auger emitters). These concerns stem from the recognition that at low exposure levels, some cells are traversed by alpha particles (or low energy electrons), whilst many cells are not irradiated. Thus, the distribution of absorbed dose at the cellular level may be very heterogeneous.

60 A number of scientists (Watt, 1989; Simmons, 1992; Katz and Cucinotta, 2003) question whether ‘dose’ is a meaningful concept for small quantities of radiation, particularly in the case of internal emitters, and consider that the averaging process becomes fundamentally progressively unsound as doses reduce. As a result it becomes meaningless to relate the health risks to ‘dose’ in the range of significance here. These scientists propose that, instead of dose, fluence (ie the number of tracks per unit area of irradiated tissue) should become the fundamental quantity in radiological protection. This does, however, have its own limitations.

61 Alternative approaches, arising from developments in microdosimetry, involving consideration of the three-dimensional interaction of ionisation tracks and DNA, may be physically more realistic, but are not yet sufficiently developed to be applied quantitatively in a manner suitable for radiological protection purposes. In any event, given the stochastic nature of cancer induction and the common assumption that the initiating event can arise from the damage associated with a single traversal of any of the target population of cells, it is not clear that an alternative formulation would be more appropriate. By definition, the risk-related dose quantities such as equivalent dose and effective dose have no meaning, and cannot be used at all, at the level of individual cells or their components. On the other hand, the physical quantity absorbed dose and its distribution amongst cells can be defined and evaluated, but the relationship to risk remains problematic. It is important to consider the mechanistic understanding provided through microdosimetry, and possible implications for risk assessment. Future developments on the nature of bystander effects (see Chapter 3) may also have implications for the delineation of cells at risk for different cancer endpoints.

62 Overall, uncertainties in dose coefficients can be regarded as small for some radionuclides (eg ^{137}Cs and ^{131}I) but substantially larger for other radionuclides, particularly when considering intakes by children or doses to the fetus (eg ^{210}Pb, ^{210}Po, ^{239}Pu and

^{241}Am). Reliable quantitative estimates of uncertainties in dose estimates for a range of radionuclides are not yet available. However, published data (Harrison *et al*, 1998; Leggett *et al,* 1998; Apostoaei and Miller, 2004) indicate that for some estimates of doses to individual tissues/organs, uncertainties may be very large, with estimates of 90% confidence intervals of an order of magnitude or more, occasionally considerably more, above and below the central estimate[20]. These uncertainties are in addition to the uncertainties in risk estimates for radiation-induced disease.

63 The NCRP (1997) has published a detailed analysis of uncertainties in risk estimates for radiation-induced fatal cancer, based on the Japanese A-bomb survivor data, including uncertainties in applying risks across populations and to low dose exposures. Its overall estimate for the 90% confidence intervals on the risk estimate show a range from a factor of 2.5–3 both below and above the 50th percentile values, corresponding to a life-time cancer risk of 1 x 10^{-2} Sv^{-1} to 8 x 10^{-2} Sv^{-1}, with a mean of 4 x 10^{-2} Sv^{-1}. Other analyses have reached similar conclusions (EPA, 1999; Goossens *et al*, 2000). Uncertainties in DDREF contributed about 40% of the uncertainty range estimated by the NCRP (1997). The Committee's consensus was that risk factors derived from the Japanese A-bomb survivor studies could be taken to lie in an uncertainty range covering an order of magnitude.

64 The ICRP has chosen not to address uncertainties in dose coefficients specifically in its publications. In the application of effective dose coefficients at doses well below limits, it may be argued that the inclusion of uncertainty bounds would add unnecessary complexity, as even with the inclusion of uncertainties such limits would not be likely to be breached. However, this is an assumption which can only be justified by consideration of these uncertainties. In the context of using dose coefficients to estimate equivalent dose to organs and tissues, which would be done if more detailed information were required for specific purposes, knowledge of uncertainties may be crucial in applying the results. The importance of recognising and attempting to quantify uncertainties in dose estimates for internal emitters is recognised by those contributing to ICRP work, and by others, as attested by recent publications on this subject (Harrison *et al,* 2001; Leggett*,* 2001, 2003).

65 Committee members agreed that the assessment of uncertainties in dose and risk estimates was important. There were differences, however, between members on the circumstances where uncertainties should be used in radiological protection. Some members considered that an explicit declaration of likely uncertainties should, wherever possible, form part of all dose and risk estimations. They remained concerned that the failure to consider uncertainties could lead to unsound scientific conclusions and policy decisions. However, all members considered that the full treatment of uncertainties might be appropriate in particular circumstances, eg in assessments of doses approaching dose limits, in specific individual dose assessments, and in the interpretation of epidemiological data.

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[20] A recent detailed analysis of uncertainties in dose coefficients from ingestion of ^{131}I, ^{137}Cs and ^{90}Sr resulted in 95% confidence intervals for organ dose coefficients for adults (males and females) of about 3–6 for ^{137}Cs (all tissues), 7–8 for thyroid dose from ^{131}I, and 20–40 for bone surface and red bone marrow doses from ^{90}Sr (Apostoaei and Miller, 2004). In a large exercise on uncertainties (Goossens *et al*, 1997), involving aggregation of uncertainty ranges obtained by a panel of experts, combined 90% confidence intervals quoted by Harrison *et al* (1998) for adult ingestion and inhalation dose coefficients varied from factors of less than ten for ^{137}Cs and ^{131}I thyroid dose, to factors of several thousand for ^{90}Sr lung dose after inhalation and ^{239}Pu bone marrow dose after ingestion. These larger ranges were partly attributable to uncertainties over the chemical forms that might be ingested or inhaled (Harrison *et al*, 1998). The estimated uncertainty ranges differed substantially between the study experts.

2.8 Conclusions

66 To the extent that ionising radiations from both internal emitters and external sources generate similar physical and chemical interactions in living matter, there are no fundamental differences between the two sources of radiation that suggest that their effects cannot be combined for radiological protection purposes. However, short-range charged particle emissions, both electron (eg low energy beta particles) and alpha particles, are important contributors to internal but not external radiation exposures. The potential heterogeneity of energy deposition in tissues resulting from these internal emitters contrasts with the relatively uniform irradiation of tissues from most external sources and defines the central difference between these two sources of radiation exposure. The Committee agreed that a methodology for combining radiation effects from both types of source should, in principle, be achievable. However, the Committee was more divided on the adequacy of methods used to take account of such heterogeneity, and these matters have been a central issue addressed by the Committee.

67 The chemical properties of an element determine its distribution and retention in body tissues and cells and hence determine the extent to which it may be located in a way that short-range emissions may have an accentuated effect (ie in terms of damage caused to cellular targets for the induction of cancer and genetic effects). Biokinetic and dosimetric models are used to determine this relationship between the distribution of radionuclides and target cells. In some cases, simple models suffice because the element and its radioisotopes are known to be uniformly distributed in body tissues and the pattern of energy deposition is similar to that resulting from external irradiation. In other cases, complex models are required to account for heterogeneous energy distribution within tissues, requiring knowledge of the location of the radionuclide at different times after intake and the location of target cells. Data available for model development are of variable quality – in some cases, particularly for some of the more important radionuclides, good information is available, including human data, but in other cases reliance is placed on sparse animal data. In many cases, there is little information on variability between individuals and within human populations. The Committee concluded that in general the combination of biokinetic and dosimetric models gave rise to estimates of central values with widely variable uncertainty ranges. The Committee was more divided on the likely span of uncertainties for specific radionuclides and situations of exposure, but there was agreement that in some cases uncertainties could extend over at least an order of magnitude.

68 The location of radionuclides within tissues is particularly important for alpha particles that typically have a range of a few tens of μm (traversing a few cells). It is also important for low energy electrons, such as the beta particle emissions from tritium with a range of <10 μm, and Auger electrons. For these radionuclides, sub-cellular location can be important, as location within the cell nucleus can increase carcinogenic potential while within cytoplasm it can decrease risk. On the basis of substantial experimental data, it is recognised that these radiation types can cause greater damage per unit energy deposition, because of the density of their ionisations in small tissue volumes, than sparsely ionising radiations such as gamma rays and X-rays, and higher energy electrons. The understanding of these differences, termed relative biological effectiveness (RBE), in terms of three-dimensional track structure, and consequent interactions with DNA and other molecules, is a key goal of microdosimetry. The Committee was generally in agreement that this field of research is not yet far enough advanced for microdosimetric techniques to present viable alternatives to current risk-related radiation dosimetry. However, there was agreement that advances in microdosimetry were likely to provide insights into the reliability of dose estimates and may ultimately provide complementary approaches. The desirability of further research was emphasised.

69 The ICRP provides comprehensive information on radiation doses estimated to result from radionuclide intake by ingestion or inhalation. The ICRP publishes biokinetic

and dosimetric models, and values of weighting factors, used to calculate quantities called equivalent and effective dose. While the models are used to give estimates of absorbed dose (Gy) to target organs, tissues, or regions within tissues, equivalent and effective dose (Sv) introduce effects-related weightings to take account of RBE (w_R) and individual tissue contributions to total risk or detriment from cancer and hereditary effects (w_T). The calculation of equivalent dose to individual tissues appears to be a simple and convenient way of combining doses from different radiation types to assess overall risk of specific cancers (or genetic effects). The further step of combining and weighting equivalent doses to give an overall whole-body or effective dose is convenient in allowing summation of all radiation exposures, internal and external, for comparison with limits for whole-body exposure. However, exclusive use of effective dose can conceal very different patterns of dose delivery from different radionuclides, both in the irradiation of specific tissues and the time-course of dose delivery. Effective doses provide no information on the likely incidence of cancer of specific types, only on the overall probability of cancer induction (ie with no distinction of type). The Committee noted, and felt that it should be more strongly emphasised, that the ICRP recommends reserving the use of effective dose for radiological protection purposes at doses below dose limits. For specific assessments, the ICRP recommends that it will sometimes be better to use absorbed dose and specific data relating to RBEs for the radiations concerned and risk factors. The Committee considered that the use of such specific information should apply when doses are, or may be, a significant proportion of dose limits, for retrospective dose assessments, and for the interpretation of epidemiological data. The Committee further concluded that it was important that the scientific basis of the ICRP methodology should continue to be challenged, and that developments in microdosimetry and radiobiology should inform judgements on their reliability.

70 Dose limits, constraints, and indeed tissue weighting factors are based largely on risk estimates for radiation-induced cancer resulting from external gamma ray exposure of the Japanese populations of Hiroshima and Nagasaki. The applicability of these risk estimates to internal exposure from short-range charged particle emissions can reasonably be questioned, given the potential complexity of the steps involved in assessing internal dose and risk. Available human data that allow quantitative estimation of risks from internal radiations, for alpha particle emitters, provide a measure of support for the use of these risk estimates. Most Committee members agreed that there does not appear to be any indication, within the limitations of the data available and the overall uncertainties in the risk estimates, of fundamental differences between internal and external radiation that cannot in principle be accommodated through the use of appropriate parameters (eg RBE and kinetic factors) in physiological models. Some members did not accept this view, and considered that there are biophysical and biochemical mechanisms that result in an enhanced effectiveness of internal emitters over external radiation in specific instances that is not taken into account in current methodology. There was agreement that enhanced effectiveness may occur as a result of radionuclide binding to DNA, but most members considered that this was an issue specific to low energy beta emitters and Auger emitters.

71 Two members argued that such instances as those quoted above occurred largely with artificial as opposed to naturally occurring radionuclides. Furthermore, they suggested that because living organisms have evolved in the presence of natural radionuclides the organisms would have adapted to their presence, which will clearly not be the case for the range of artificial radionuclides. For these reasons, these members felt that artificial radionuclides, as a class, were likely to present an enhanced risk. However, the other members of the Committee did not concur with this view.

72 Committee members agreed that insufficient attention has been paid in the past to uncertainties in dose and risk estimates for internal emitters. Reliable quantitative estimates of uncertainties in dose coefficients for a range of radionuclides are not yet

available. Uncertainties in estimating equivalent dose, which combine the uncertainties in estimating both absorbed dose and RBE, are always likely to be significant, and probably vary in magnitude from around a factor of two or three above and below the central estimate in the most favourable cases (ie where good data were available) to well over a factor of ten in unfavourable ones (ie where they were not). For effective doses, there are additional uncertainties in the use of tissue weighting factors. Further work is required to quantify uncertainties in dose estimates for important radionuclides, with transparent identification of all the underlying contributions to overall uncertainties and how to compound them. The Committee concluded that it was important that doses and risks from internal emitters should be calculated on the basis of best current information, using central values, and with no bias towards 'conservatism' or 'pessimism' (as is sometimes implied). Introduction of such subjective considerations had no place in an objective assessment. The Committee agreed that, where appropriate, dose and risk estimates should be combined with an appreciation and explicit statement of the uncertainties involved. This approach would help identify those situations in which a precautionary approach might be appropriate, and was greatly to be preferred over one in which conservative/pessimistic estimates were arbitrarily introduced at various stages in the calculation.

ANNEX 2A
Microdosimetric Considerations

Introduction

(1) The interactions of radiation in matter are by their nature probabilistic (stochastic) and therefore they lead to an infinite diversity of patterns of energy deposition when viewed at the atomic or molecular level. At this level of resolution, the patterns are dominated by the detailed structures of the individual radiation tracks, which consist of the molecular ionisations and excitations along the paths of the charged radiation particles. In the case of internal emitters, the charged particles are predominantly the emitted beta particles and alpha particles and the secondary electrons that they produce in both cases. The gross inhomogeneities within and between the radiation tracks are reflected to a decreasing extent when viewed at decreasing levels of resolution, up through cellular dimensions to tissues and organs. Absorbed dose is an average macroscopic quantity within a defined mass (or volume) and it takes no account of the spatial distribution of the energy deposition within the mass. Therefore, the use of absorbed dose in tissue, and also its extension to the ICRP risk-related quantities derived from it for organs (equivalent dose) or the body (effective dose), makes the implicit assumption that the average provides sufficient information for the practical application under consideration. One inadequacy of this assumption is well recognised, and partially compensated for by the ICRP, by the introduction of the radiation-weighting factors, w_R (previously quality factors, Q), to take some account of the average differences in biological effectiveness of radiations of grossly different types of track structure.

(2) It has long been recognised that the microscopic, stochastic features of radiation energy deposition are relevant to understanding the mechanisms of radiation action and consequent biological effects. The field of 'microdosimetry'[21] emerged in the 1960s. The growth and emphasis of the field is reflected in the proceedings of the series of international symposia on microdosimetry, which started in 1967 and has continued to the most recent 13th symposium in 2001. The term 'microdosimetry', in its general sense, refers to radiation events and their effects within microscopic volumes that are dominated by the stochastic properties of radiation and are not well represented by the average macroscopic quantity absorbed dose alone. A few examples of the application of microdosimetry at different levels of resolution are:

a the distribution of hits to individual cells, or cell nuclei, adjacent to the lung airways from exposure to inhaled radon and its decay products, over dimensions of 10–100 μm (NRC, 1999);

b the distribution of absorbed dose (energy per unit mass) to individual cells and major cell compartments from internal emitters, particularly in the context of nuclear medicine, over dimensions down to ~10 μm (Goddu *et al*, 1996);

c the use of low pressure proportional counter measurements (see below), simulating microscopic tissue volumes down to ~1 μm, to identify practical radiation-quality-related features of radiotherapy fields (Herskind *et al,* 2002) or

[21] A useful working definition of 'microdosimetry' has been suggested as 'the study of the physical microscopic properties of ionising radiations, their interactions and their patterns of energy deposition, with particular emphasis on the inhomogeneities and stochastic nature of the interactions. This is in contrast to conventional dosimetry, which is based on average macroscopic quantities such as absorbed dose. In many situations absorbed dose is totally inadequate to describe radiation action in biological, or other, material because the mechanisms and effects are dominated by the inhomogeneous microscopic properties, especially at cellular or subcellular dimensions' (Goodhead, 1987).

for construction of radiological protection instruments for mixed fields (Waker *et al,* 2002);

d the spectrum of damage to intracellular DNA as the result of random exposure to radiations of different types and energies, over dimensions ~2–10 nm (Nikjoo *et al*, 1997, 2001).

(3) The possible biological implications of passages of radiation tracks through, and inhomogeneities of energy deposition in, a wide range of volumes from DNA (~2 nm) to individual cells (~10 μm) and small regions of tissue (~ 100 μm), gave rise to considerable debate within the Committee. Three classes of radioactive materials have been considered by the Committee in some detail: soft beta emitters, Auger emitters and alpha emitters. Soft beta particles are electrons emitted with very low energies from the nuclei of certain atoms, of which the most important in the present context is tritium (see Annex 2B). Auger emitters again give off low energy electrons but by a completely different (atomic) mechanism and many of the Auger electrons are of particularly low energy and short range. For the weakest of these, the range is comparable with the diameter of the DNA molecule and so it becomes essential to know where in the cell the emitter is to be found (see Annex 2C). Alpha particles are the nuclei of helium atoms which are given off by elements such as radon and plutonium. They have ranges of a few cell diameters, and so knowledge of the location of the emitter is required at cellular rather than molecular level (see Annex 2D and Chapter 3).

'Proportional-counter' Microdosimetry

(4) The 1983 report of an ICRU/ICRP task group focused particularly on the proportional-counter approach and made proposals for its application in radiological protection. These proposals were made on the assumption that mean quantities measured at the ~1 μm level provided a better description of radiation quality than did the quantity LET that is conventionally used by the ICRP in defining radiation quality factors and radiation weighting factors (ICRU, 1983). Based on information from early measuring devices known as Rossi proportional counters, which can simulate tissue volumes of diameter ~1–10 μm, ICRU Report 19 (1971) defined quantities for use in this branch of microdosimetry, as follows.

(5) The statistical quantity 'specific energy', z, is the quotient of ε by m, where ε is the energy imparted by ionising radiation to the matter in a volume element of mass m,

$$z = \varepsilon / m.$$

The statistical quantity 'lineal energy', y, is the quotient of ε by d, where ε is the energy imparted to matter in a volume during an energy deposition event and d is the mean chord length in that volume,

$$y = \varepsilon / d.$$

The absorbed dose D was re-defined as the quotient of $\mathrm{d}\bar{\varepsilon}$ by $\mathrm{d}m$, where $\mathrm{d}\bar{\varepsilon}$ is the mean energy imparted to the matter in a volume element of mass $\mathrm{d}m$,

$$D = \mathrm{d}\bar{\varepsilon} / \mathrm{d}m.$$

Thus, specific energy and lineal energy are stochastic quantities in an irradiated tissue. Their measurement in radiation fields highlighted the great variability of energy deposition on the micrometer scale. The mean values of the frequency distributions of specific energy and lineal energy for single radiation events provide microscopic analogues of absorbed dose and LET, respectively, in the micrometer-sized volumes of specified size and shape.

Hit Frequencies

(6) Based on measurements and calculations of specific energy of single events in 7 μm spheres, to represent individual cells in the body, Bond (1981) noted that, because at low levels of radiation (ie those of significance in radiological protection) a large proportion of the cells will have received no radiation, the mean dose per cell represented by the average tissue dose is not the same as the mean dose per dosed cell. He suggested that this distinction is important for stochastic processes such as induction of cancer by low level radiation because it is the effect within a cell (or a small number of cells) that is important.

(7) Others have suggested that a better quantity to use in this context is the fluence of charged particles through the critical volume (cell). It is only when most of the cells have received several hits per cell (ie at absorbed doses above several mGy for low LET radiation and about a gray for high LET radiation) that dose becomes a suitable surrogate for charged particle fluence. Experimental verification of these ideas was obtained for the case of alpha particle irradiation of lung tissue by Simmons and Richards (1989), as described in Annex 2D below. However, the use of fluence to relate to biological effects would require additional specification of the types and energies of the radiation particles at the point of interest and clarification of what fluence is to be used for low LET radiations (eg fluence of photons, primary electrons or secondary electrons above some specified energy). Also required for risk estimation would be relationships between these fluences and cancer incidence based on epidemiological observations.

(8) Report 36 of the ICRU on microdosimetry in 1983 suggested that the term ‘low dose’ could imply a situation in which <20% of the targets exposed are actually hit by the radiation. If one makes the simplifying assumption that the nuclei of the cells can be represented by spheres of diameter 7 μm and that the LET of the alpha particles is 100 keV μm^{-1}, it can be shown that this definition of ‘low’ results in a limiting tissue absorbed dose of about 80 mGy. But, by contrast, at this dose all nuclei are hit when subject to low LET radiation. The question has therefore been raised of the meaning of RBE, conventionally expressed as a ratio of absorbed doses for equal biological effect, and hence the weighting factors inferred from its measurement in relevant biological systems. Although it was clearly impossible to make any specific recommendations, the Committee felt that these factors should be borne in mind when attempting to assess the risks associated with internal emitters and ionising radiation generally.

ANNEX 2B
Tritium Doses and Risks

Introduction

(1) The Committee gave particular attention to considerations of the adequacy of ICRP dose coefficients for tritium and evaluation of the effects of tritium as an internal emitter. This included consideration of a recent paper by Harrison *et al* (2002), examining uncertainties in dose coefficients for exposures to tritiated water (HTO) and organically bound tritium (OBT), and a number of internal papers from the Committee, two dealing with the same topic as Harrison *et al*, and one examining the chemistry of tritium compounds and the characteristics of tritium's radiation at a cellular/sub-cellular scale. As part of this review, alternative viewpoints were considered, including the suggestion that the ICRP dose coefficient for ingestion of HTO by adults is an underestimate by a factor of ten. The special case of tritiated DNA precursors was also considered.

(2) Tritium (^{3}H) is a radioisotope of hydrogen (^{1}H) with a half-life of 12.3 years. It decays with the emission of a beta particle to an isotope of helium – ^{3}He. The beta emission is of unusually low energy, the average and maximum energies being 5.7 and 18.6 keV, respectively. It is both man-made and naturally occurring. The average range of the emitted beta particle in water (or biological tissues) is about 0.5 μm, considerably less than the typical diameter (5–20 μm) of a cell or even a cell nucleus. Therefore the sub-cellular location of tritium atoms is of importance in determining the effects of its beta decay. Furthermore, because of its low initial energy and short range, the average density of ionisation produced by the passage of a tritium beta particle (mean LET = 12.1 keV μm^{-1}) is higher than that for a moderate/high energy beta particle. For example, the mean LET for ^{90}Sr is 0.52 keV μm^{-1}. Thus, although tritium is normally classified as a 'low LET' beta emitter, in reality its beta emission is intermediate between a more typical low LET emission (~0.5 keV μm^{-1}) and the high LET of an alpha particle. For example, a 5 MeV alpha particle would have a range of ~45 μm, and a mean LET of ~100 keV μm^{-1}.

(3) Tritium might be regarded as an extreme case of a radionuclide for which the chemical speciation is crucial in determining the effects of its radioactive decay. This is because of the very wide range of compounds in which the tritium atom may be firmly bound, coupled with the unusually short range of its emitted beta particle. As an isotope of hydrogen, tritium can be a constituent atom in the water molecule and in every organic compound. Generically, these are referred to as HTO (tritiated water) and OBT (organically bound tritium), respectively.

(4) When bound in water, and in some organic compounds, the tritium atom is highly labile, exchanging readily and rapidly with other similarly labile hydrogen atoms. In a biological system, the instantaneous chemical location of the exchangeable tritium fraction is likely to be unimportant, as the tritium will be rapidly exchanging and uniformly distributed throughout the medium. However, in many organic compounds, many of the hydrogen (and therefore tritium) atoms are firmly held and are non-exchangeable. In such compounds, tritium may become fully or partially 'fixed', and only be released – to become part of the exchangeable pool – by metabolic transformation of the particular molecule in which it is sited.

(5) Thus, tritium can be present in organic molecules in exchangeable and non-exchangeable forms depending on the chemical bonds involved. In most organic molecules, the majority of tritium atoms bound to oxygen, nitrogen, or sulphur atoms can be readily exchanged with hydrogen in body water and will exhibit kinetics similar to HTO. However, tritium atoms which replace H atoms in C–H bonds are not exchangeable in this way: these are only released by enzymatically-controlled metabolic reactions. The term OBT is commonly applied to tritium incorporated into the major dietary constituents of

carbohydrates, proteins and lipids. But the term applies to all organic molecules, including labelled nucleic acids, which may exhibit a very different behaviour to that of tritiated water in body tissues.

ICRP Dose Coefficients

(6) The ICRP provides models and calculates dose coefficients for intakes of tritium as HTO or OBT (ICRP, 1989, 1993). The models consider intakes of HTO and OBT by ingestion and inhalation by adults and children, as well as doses to the fetus following intakes by the mother. The models make a number of simplifying assumptions. First, it is assumed that absorption to blood is complete and that tritium is subsequently distributed uniformly throughout body tissues. Second, retention in body tissues is represented by two components, the first corresponding to the turnover time of body water and the second to the turnover of carbon, with shorter retention times of both components in younger children. The first component corresponds to HTO and tritium exchangeably bound to organic molecules and essentially in equilibrium with body water, and the second component corresponds to non-exchangeably bound OBT. The ICRP does not give dose coefficients for specific forms of OBT (eg ^{3}H-DNA precursors). Dose coefficients for intakes of OBT are generic values for application to, for example, unspecified dietary intakes.

Adequacy of ICRP Dose Coefficients

(7) Harrison *et al* (2002) reviewed the experimental and human data on which the current ICRP dose coefficients for HTO and OBT are based and assessed the reliability of the dose coefficients in terms of uncertainties in central estimates for population groups. The analysis included uncertainties in the absorption of OBT to blood, incorporation of tritium into OBT in body tissues, retention times in tissues, transfer to the fetus and the relative biological effectiveness (RBE) of tritium beta emissions compared with gamma rays. Heterogeneity of dose within tissues and cells was also considered in the paper. The results of this analysis were 5% to 95% uncertainty ranges on the central values of doses per unit intake for adults of about a factor of 3 for HTO and about 5 for OBT, with greater uncertainties for doses to children and the fetus. The central (50%) values from these distributions were about twice the corresponding ICRP values, largely because of the inclusion of a range of 1 to 2.5 for tritium's RBE. The consideration of OBT in this analysis applied to general dietary intakes and it was made clear that specific organic forms including DNA precursors should be considered on an individual basis.

(8) A second paper on tritium considered by the Committee drew attention to a number of unique properties of tritium including its propensity to exchange with hydrogen atoms in the biosphere, its ability to bind with organic molecules via metabolic reactions, its rapid distribution as water in the environment, substantial evidence of RBE values greater than one, and related microdosimetric considerations. The later version of this paper suggested that the current ICRP dose per unit intake values for tritium were too low by a factor of about ten, rather than two as suggested by the Harrison *et al* paper. This arose from increasing tritium's radiation weighting factor from one to between two and three; recognising the long retention times in the body of OBT which arose from HTO intake; and recognising microdosimetric considerations, including the high levels of dense ionisations from tritium decay tracks.

(9) The Committee considered a third paper on tritium which also drew attention to the inconsistency between the evidence for tritium's RBE and its current radiation weighting factor of one. This evidence came from three sources. First was an understanding of the physical effects of radiation. Second were the theoretical calculations based on LET by the ICRU (1986) which also supported an RBE of two for tritium. Third was the abundant experimental evidence from RBE studies which pointed to an RBE for tritium of between two and three. This paper also expressed concern at the evidence of preferential uptake

of tritium from the environment, including large concentration factors of tritium in fish relative to sea water (>10^4), considered to be attributable to OBT discharges of tritiated biological precursors into Cardiff Bay.

(10) The Committee was informed that the latest review by the ICRP (2003) of RBE values had not considered the RBE evidence on tritium, and that the ICRP had maintained its previous view that w_R should be one for all photons and electrons, including tritium beta emissions. This matter is considered further in paragraph 13 below.

Tritiated DNA Precursors

(11) The ICRP dose coefficients for OBT do not apply to intakes of specific organic forms of tritium. The potential for tritiated DNA precursors to result in substantially higher doses and effects than other forms of tritium has long been recognised and has received considerable attention in terms of experimental studies and theoretical considerations (eg ICRP, 1979; NCRP, 1979). The Committee considered evidence on this subject, most of which relates to *in vitro* and *in vivo* studies using tritiated thymidine (^{3}HTdR). For example, in studies of *HPRT* mutation in cultured mouse cells, Ueno *et al* (1989) reported a difference of a factor of two between RBE values for ^{3}HTdR and HTO; values for ^{3}H–amino acids and HTO were not significantly different. This comparison was based on estimates of dose to cell nuclei and converts to a factor of six on the basis of average cell dose. The factor of two difference in effect on the basis of nuclear dose might be attributable to transmutation effects (the chemical effect of change from ^{3}H to ^{3}He), or to regional distribution of dose within the nucleus. It was noted that no difference was observed between (6–^{3}H) and (methyl–^{3}H) thymidine, despite expected differences in their transmutation effects.

(12) Theoretical assessments of the relative risks of different DNA and RNA precursors (NCRP, 1979), based on considerations of their biochemistry and cell kinetics, suggested that the toxicity of ^{3}HTdR could be taken as representative of other precursors with the exception of 5-^{3}H-deoxycytidine (5-^{3}HCdR). It was suggested that the toxicity of 5-^{3}HCdr should be assumed to be twice that of ^{3}HTdR on the basis of differences in transmutation effect.

Conclusions

(13) The Committee accepted that there was much evidence from radiobiology theory and from RBE experiments that tritium's RBE was greater than 1. Considering all observed effects of HTO exposure, RBE values were in the range of 1–3.5. For comparisons with gamma rays most values were from 1–3, while for X-rays most were from 1–2, with values of 1–1.5 predominating. These measured RBEs for tritium beta irradiation are reasonably consistent with estimates based on microdosimetric considerations. Some Committee members referred to studies of carcinogenesis in animals as being most relevant to the estimation of tritium RBE for cancer induction in humans. Studies of mammary tumorigenesis and acute myeloid leukaemia in mice had resulted in values of about 1 compared with X-rays (Gragtams *et al*, 1984; Johnson *et al*, 1995). Members differed in their views on the implications of tritium RBE data for the use of w_R in ICRP calculations of equivalent doses from tritium. Some supported the use by the ICRP of a single w_R value of 1 for all low LET radiations for general radiological protection purposes, while others considered that the ICRP should routinely apply a w_R of 2 or greater to tritium beta emissions.

(14) Some Committee members considered that factors additional to RBE have been neglected in ICRP models for tritium and current dose coefficients may be underestimates by a factor of about 10. Those members who had contributed to the ECRR (2003) report pointed to w_R values for tritium of 10–30 (see text of Chapter 2). Other members

concluded that ICRP dose coefficients for HTO were not substantial underestimates, but noted that values for OBT must be used with caution since they may well not apply to specific materials.

(15) Several Committee members concluded that risks from tritiated DNA precursors were reasonably well understood on the basis of reliable experimental data, but others disagreed. Some members expressed concern about the possibility of environmental concentration of tritium contained in specific stable organic compounds and the potential for high RBE of tritium incorporated into DNA. A number of members considered that more research should be carried out on tritium microdosimetry.

ANNEX 2C
Auger Emitter Doses and Risks

(1) The Committee considered the problem posed by Auger emitters, noting that current ICRP methodology takes no account of the increased RBE of DNA-bound Auger emitters.

(2) Auger electrons have energies ranging from about 10 eV to 10 keV, that are most commonly emitted by radionuclides that decay by electron capture (EC), internal conversion (IC) or isomeric transition (IT). The yield of electrons is dependent on the radionuclide, with, for example, 5 and 25 electrons released on average per decay of ^{55}Fe and ^{125}I, respectively. The proportion of the total decay energy due to Auger electrons varies between radionuclides; for example, Auger emissions account for 72%, 12% and less than 1% of the total decay energy of ^{55}Fe, ^{125}I and ^{99m}Tc, respectively. Because of the extremely short ranges (of the order of 1 nm to 1 μm) of Auger electrons in tissues, their location within cells is important in determining the extent of DNA damage. Table 2C.1 compares dose to the cell nucleus for Auger-emitting nuclides for different assumptions regarding their cellular location. If the radionuclide is confined to the cytoplasm, conventional dosimetry will overestimate dose to the nucleus. However, if the radionuclide concentrates in the nuclei of cells, there is the potential for significant underestimation of dose using conventional dosimetry.

Table 2C.1 Calculated ratio of dose to the nucleus

Assuming concentration of all activity in the specified region compared with the assumption of uniform distribution. Cells are assumed to have a nuclear radius of 4 μm and a cell radius of 12 μm (from Faraggi *et al,* 1998).

Nuclide	Cell membrane	Cytoplasm	Nucleus
^{99m}Tc	0.82	0.85	6.8
^{125}I	0.74	0.86	7.4
^{111}In	0.80	0.89	5.8
^{67}Ga	0.81	0.86	7.3
^{201}Th	0.61	0.73	11.7

(3) The biological effects of Auger emitters have been extensively studied in a variety of *in vitro* and *in vivo* experimental systems. *In vivo*, rodent spermatogenesis has been utilised as a model system to evaluate the cytotoxicity of a range of Auger emitters including ^{55}Fe, ^{99m}Tc, ^{111}In, ^{114m}In, ^{123}I, ^{125}I and ^{210}Tl. *In vitro*, the cytotoxic effects of ^{35}S, ^{75}Se, ^{51}Cr, ^{67}Ga and ^{77}Br, and a range of compounds labelled with ^{123}I and ^{125}I, have been studied in a variety of human and rodent cell lines and model culture systems. Representative of results obtained are observations using ^{125}I of high RBE values of seven to nine for cell killing when the nuclide is incorporated into DNA in the form of ^{125}I-iododeoxyuridine (^{125}IUdR), values of around four for ^{125}I localised in the nucleus but not directly bound to DNA, and values of around one when ^{125}I is localised in the cytosol.

Significant Auger Emitters

(4) Auger emitters which satisfy the following criteria are considered to be significant in terms of radiological protection. That is, Auger emitters:

a which occur in significant quantities, either naturally or in environmental discharges or in nuclear medicine;

b in which a significant percentage of their decay **numbers** are via the Auger process;

c in which a significant percentage of their decay **energies** are via the Auger process;

d which emit a large number of Auger electrons from a single decay, allowing substantial overlap of electrons within the first few nanometres from the point of decay;

e for which there is evidence of concentration in cell nuclei or, in the case of extremely low energy Auger electrons, in DNA.

A number of Auger emitters, both natural and man-made, are present in the environment (see Table 2C.2). However, exposure to these radionuclides appears to be at very low levels. Of more consequence is the use of Auger-emitting radionuclides in nuclear medicine, where activities administered can be relatively high.

(5) Auger emitters pose difficult questions about the existing dosimetric conventions used in ICRP dose models including the assumption of homogeneous distributions of nuclides and their energies in organs and cells. A number of authors (see Hofer, 1998) discuss alternative dosimetry systems. Bingham *et al* (2000) refer in particular to the scheme used by the American Association of Physicists in Medicine (AAPM) (Howell, 1992; Sastry, 1992) which recommends a w_R of 20 for all Auger emitters for stochastic effects, for the proportion bound to DNA. Using this scheme, and assuming 100% binding to DNA, Goddu *et al* (1996) considered the example of doses delivered within the testes from ^{67}Ga, ^{99m}Tc and ^{125}I, and showed that conventional dosimetry would underestimate this self-dose by factors of about 4, 2 and 8 times, respectively. Actual increases in equivalent dose would be lower than calculated by Goddu *et al* (1996) because cross-fire doses from penetrating radiations from other tissues were not taken into account in this analysis. The AAPM method was also applied by Bingham *et al* (1997) to estimate equivalent doses to the prostate from ^{51}Cr and ^{65}Zn, assuming that the proportions bound to DNA were 0.5 and 0.2, respectively. Doses were greater than those calculated conventionally by factors of 1.5 for ^{51}Cr and 3 for ^{65}Zn.

(6) An additional consideration raised by Bingham *et al* (1997) is that conventional dosimetry does not account for the heterogeneous distribution of radioactivity between cells within tissues which could be important if the sensitive cells for cancer induction were not uniformly distributed in the tissue.

Conclusions

(7) Committee members were agreed that the possibility of increased risk from Auger emitters on the basis of cellular location and non-uniform distribution between cells within tissues should be examined for individual radionuclides and chemical forms of concern. This would involve experimental studies of distribution, together with studies of biological effects for those radionuclides/chemical forms showing significant presence in cell nuclei. The ICRP recognises these uncertainties for Auger emitters and has stated in ICRP Publication 92 (2003) that they represent a special case and will need continued special attention.

Table 2C.2 Occurrence and physical characteristics of Auger emitters (from Bingham *et al*, 2000; with addition of ^{137m}Ba)

Nuclide	Half-life	% of total decay energy Augers	keV per Auger decay	Occurrence
^{41}Ca	1.4 x 10^5 y	84.8	2.3	Solid nuclear waste
^{55}Fe	2.7 y	71.9	4.2	Solid nuclear waste
^{59}Ni	7.5 x 10^4 y	65.4	4.6	Solid nuclear waste
^{94}Mo	3.5 x 10^3 y	34.2	5.5	Solid nuclear waste
^{113}Sn	115 d	21.1	6.2	Liquid discharges
^{137m}Ba (daughter of ^{137}Cs)	2.55 m	9.8	0.65	Liquid discharges Air emissions NP, NW tests
^{83m}Kr	1.8 h	9.6	4.0	Air emissions
^{109}Cd	464 d	9.2	10.1	Industrial use
^{93m}Nb	13.9 y	8.3	2.5	Solid nuclear waste
^{121m}Sn	55 y	8.1	3.1	Solid nuclear waste
^{125m}Te	58 d	7.8	11.3	NW tests
^{103m}Rh	56.1 m	7.1	2.8	NP, NW tests
^{134m}Cs	2.9 h	6.1	8.4	NP, NW tests
^{57}Co	271 d	5.6	18.6	Liquid discharges
^{169}Yb	32.0 d	5.0	21.6	NP, NW tests
^{133}Xe	5.2 d	2.2	4.0	Air emissions
^{132}Te	78.2 h	1.8	6.1	Liquid discharges
^{140}Ba	12.7 d	1.3	6.4	NW tests
^{144}Ce	284 d	0.9	1.0	NP, NW tests
^{143}Ce	33 h	0.8	5.5	Liquid discharges
^{65}Zn	244 d	0.8	4.7	Liquid discharges
^{141}Ce	32.5 d	0.5	1.3	Liquid discharges
Medical				
^{125}I	60.1 d	19.9	12.2	
^{201}Tl	3.0 d	11.0	15.3	
^{129}I	1.6 x 10^7 y	7.0	6.2	
^{123}I	13.2 h	3.7	7.4	
^{67}Ga	78.3 h	3.1	6.3	
^{111}In	2.83 d	1.6	6.8	
^{99m}Tc	6.02 h	0.6	0.9	
Naturally occurring (daughters of U series, and ^{40}K)				
^{210}Pb	22.3 y	13.8	5.9	
^{228}Ra	5.75 y	12.8	2.2	
^{231}Th	25.5 h	8.7	16.5	
^{234}Th	24.1 d	2.9	2.0	
^{212}Pb	10.6 h	1.4	4.5	
^{228}Ac	6.13 h	0.6	8.3	
^{40}K	1.28 x 10^9 y	<0.01	0.2	

NP: nuclear power; NW: nuclear weapons.

ANNEX 2D
Alpha Emitter Doses and Risks

Introduction

(1) The Committee considered doses and risks from alpha-emitting radionuclides in a number of contexts. Human data allowing comparisons of cancer risks from alpha-emitting radionuclides and external radiation were presented to the Committee in a paper by Harrison and Muirhead (2003), as discussed in the main text. The suggestion that heterogeneous distribution of alpha emissions in tissues, particularly from particulate sources, will lead to enhanced 'hot' particle effects was addressed in a paper prepared for the Committee and subsequently published (Charles *et al*, 2003). The conclusions of this review are discussed in Chapter 3 and referred to below. In addition, the Committee examined a suggestion that inhaled particles containing radionuclides, particularly alpha emitters, may be transferred to the fetus and present a hitherto neglected leukemogenic risk. Discussion of this possibility is outlined in the main text and expanded below.

Heterogeneous Dose from Alpha Emitters

(2) Although a large number of papers have been published over a 20-year period on the application of microdosimetry to internally deposited alpha emitters, time constraints prevented the Committee from considering these in detail. However, Professor Simmons did present some of his own work on the distribution of energy depositions from alpha particles crossing lung cells following the trapping of plutonium dioxide particulates in the deep lung. This showed that, for low activity particulates giving rise to small doses to the tissue overall, the range of energy depositions could vary by four orders of magnitude. Furthermore the shapes of the distributions were different when measured for the tissue overall, the individual cells, or the nuclei within the cells. Hence the dose, defined by the mean value of the distribution, would be different for each case. Professor Simmons argued that it would therefore be meaningless to attempt to relate any biological effect to this quantity.

(3) However, the conclusion reached by Simmons appears to contrast with indications from other studies. As discussed by Harrison and Muirhead (2003), similar risk estimates for radiation-induced lung cancer in humans have been derived for very different alpha particle exposures from radon (occupational and residential) and plutonium particulates (Mayak workers) and from external low LET radiation (A-bomb survivors). Taking account of alpha particle RBE, the risk estimates derived were similar despite differences including the time-course of dose delivery and the heterogeneity of energy deposition from ^{239}Pu oxide particles. On the specific issue of risks from local 'hot' particle alpha irradiation of tissues, animal studies of chromosomal aberrations and cancer in liver after administration of different sized ^{239}Pu oxide particles or ^{239}Pu citrate suggested that effects are related to average tissue dose (Brooks *et al,* 1974, 1983; Barcellos-Hoff and Brooks, 2001). The authors estimated that all cells would experience alpha track traversals after administration of ^{239}Pu citrate for the smallest particles, compared with fewer than 1% of cells for the largest particles. Similarly, comparisons of risk estimates for radiation-induced liver cancer and leukaemia in humans after heterogeneous tissue exposures to alpha emissions from Thorotrast or uniform low LET radiation exposures show no evidence of unexpected enhancement of effect due to 'hot' particle irradiation. The overall conclusion of the review by Charles *et al* (2003) was that the ICRP use of average tissue dose was likely to provide a reasonable estimate of cancer risk, within a factor of three either way. However, some Committee members pointed out that by necessity the available data concerned doses at which effects could be observed and did not preclude the possibility that there may be a potential enhancement of effect at lower doses from lower activity 'warm' particles.

Transfer of Inhaled Particles to the Fetus

(4) The behaviour of inhaled particles was extensively reviewed by the ICRP (1994). Alveolar epithelial cells contain endocytic vesicles, about 0.1 μm in diameter. These are responsible for the passage of specific macromolecules from blood and between cells, but may provide a route of uptake of smaller particles (<0.1 μm diameter) into interstitial tissue and thence to the lymphatics, not directly to blood (Lehnart *et al*, 1986). Most particles, however, are cleared by phagocytic uptake by alveolar macrophages (see, for example, Brain, 1988). Most are carried up to the bronchioles where they are cleared from the lungs in the mucociliary current. Other macrophages migrate through the alveolar epithelium and reach the lymphatics. There is evidence that very small particles may enter blood directly after inhalation. Stradling *et al* (1978a, 1978b) found that 1 nm particles of $^{239}PuO_2$ or $^{238}PuO_2$ were rapidly transferred to blood while transfer of 25 nm particles was negligible, consistent with passage of the 1 nm particles by passive diffusion through membrane pores (maximum 4 nm diameter) in capillary endothelial cells. The tissue distribution of plutonium reaching blood was consistent with particle dissolution, that is, retention mainly in skeleton and liver.

(5) Particles reaching the lymphatic system are accumulated and avidly retained in tracheobronchial (TB) lymph nodes. Animal data and human autopsy data show long-term accumulation of plutonium oxides and similar materials in TB lymph nodes. A small proportion of particles may eventually reach blood, and this fraction may be greater when the lymph nodes are heavily loaded or damaged (Oberdorster, 1988).

(6) Particles reaching blood are efficiently removed by phagocytic cells in the liver, spleen and bone marrow, resulting in long-term retention. This is exemplified by the distribution and retention of Thorotrast (colloidal ^{232}Th oxide) in humans (see above). Thus, any uptake by the placenta would have to compete with this process.

(7) The placenta presents a selective barrier to control the passage of nutrients from the maternal circulation to the fetal circulation and the passage of excretory products in the reverse direction. Materials with molecular weights >500 dalton show progressively reducing capacities for passive transfer from maternal circulation to the fetus (Pacifici and Nottoli, 1995). It is clear, however, that in specific circumstances higher molecular weight compounds are transferred from maternal circulation to the fetus by the active process of endocytosis. This mechanism applies principally to maternal proteins such as immunoglobulins, insulin and transcobalamin-Vitamin B12 complex that are required for fetal development (Moestrup *et al*, 1996; Desoye *et al*, 1997; Ellinger *et al*, 1999). Endocytic processes are driven by the expression of domain-specific protein receptors in placental cell membranes – these serve to identify the proteins that are required, others are excluded. However, as in the movement of particles from alveoli in the lung, it is possible that smaller particles of <0.1 μm diameter may be transferred to some extent by this process. Such non-specific uptake of radioactive materials, including particulates, has been demonstrated for the yolk sac membrane in rodents and primates and the neonatal intestine in rodents (Sullivan, 1980; Sikov, 1987). However, subsequent transfer from the yolk sac to the developing embryo and from neonatal intestinal enterocytes to blood is relatively low and, in the case of insoluble materials, appears to reflect the extent of dissolution within the cells of these membranes.

(8) Prosser *et al* (1994) measured fallout ^{239}Pu in human fetal tissues obtained from second trimester terminations in the UK, using mass and alpha spectrometry. Fetal tissue concentrations of a few tens of $\mu Bq\ kg^{-1}$ were reported. Corresponding average concentrations in young adults are around 1 $mBq\ kg^{-1}$, with greatest concentrations in liver, bone, lungs, and particularly TB lymph nodes (Popplewell *et al*, 1985). These results are consistent with expectations of the behaviour of inhaled plutonium particles – movement of dissolved plutonium via blood, mainly to liver and skeleton, and lymphatic drainage of undissolved particles to TB lymph nodes. Low availability of plutonium for

uptake by the placenta reflects low levels of plutonium in blood, bound to the plasma protein, transferrin. Some of the fetal tissue samples were also analysed for the naturally occurring radionuclides, ^{210}Po, ^{232}Th and ^{238}U (Prosser *et al*, 1994; Bradley and Ewings, 1995). Concentrations of ^{210}Po were around 1000 times greater than ^{239}Pu concentrations. Those of ^{232}Th and ^{238}U were substantially lower than ^{210}Po concentrations but greater than ^{239}Pu concentrations. Maximum doses to the fetus were estimated as about 20 μSv from ^{210}Po, 1 μSv from ^{232}Th, 3 μSv from ^{238}U, and 0.02 μSv from ^{239}Pu. Henshaw *et al* (1995) measured concentrations of naturally occurring alpha-emitting nuclides in fetal tissues including vertebrae, using autopsy samples obtained at various stages of development from 18 weeks to term (38 weeks). They showed that maximum concentrations of ^{210}Po, measured in bone samples, were up to 180 mBq kg^{-1} in late gestation (Purnell *et al*, 1999). Total alpha dose to the fetal bone marrow from all nuclides was estimated as 24 μSv. It was concluded that the probability of stem cells receiving more than one alpha particle hit was extremely low.

Conclusions

(9) There was no consensus among members regarding the risks posed by localised 'hot' particle irradiation. Some members considered that particles with a particular content of an alpha emitter ('warm' particles) must be more hazardous than more uniform distribution of the same activity. Others were not persuaded by this argument.

(10) Committee members agreed that the available data on the behaviour of radioactive particulates in the body do not support the proposal that they transfer readily to the fetus and pose a high risk of *in utero* leukemogenesis. However, the extent of possible risk was not agreed and individual members pointed to research in progress that might provide additional data. It was also noted that the ICRP model of the respiratory tract was deficient in not taking account of the recognised lymphatic movement of particles to the general circulation.

3 Biological Evidence

3.1 Introduction

1 In accordance with its remit, the Committee examined evidence from biological studies on a number of matters, including genomic instability, bystander effects, minisatellite mutations, particulates, adaptive responses, and microdosimetric considerations as evidenced by various internal emitters. It also examined a number of hypotheses and assertions that current biological and dosimetric models substantially underestimated risks from exposures to internal radiation. The biological evidence of most interest to the Committee related to assertions that current models substantially underestimated risks of internal irradiation. This evidence concerned damage mechanisms either particular to internal irradiation or more important for internal radiation than for external radiation.

3.2 Genomic Instability

2 Radiation-induced genomic instability may be defined as a process whereby radiation damage to a cell destabilises genomic DNA resulting in the ongoing appearance of a host of potentially detrimental effects in the progeny of the irradiated cell, many cell divisions after the initial insult. Genomic instability is characterised by genetic changes including chromosomal rearrangements, micronuclei, transformation, gene amplifications, gene mutation, reduced plating efficiency (lethal mutations or delayed reproductive cell death) and developmental abnormalities *in vivo* (reviewed in Little, 1998; Morgan, 2003a, 2003b; Morgan *et al*, 1996; Pils *et al*, 1999). Although data are limited, there is some evidence that the induction of instability does not demonstrate a linear relationship to dose but is maximally induced by the lowest doses investigated, including a single alpha particle traversal (Kadhim *et al*, 1992, 2001) and can lead to a substantially greater frequency of mutations than that induced by the direct action of radiation and expressed in the first one or two cell generations. Post-irradiation genomic instability is not universally expressed in mammalian cells *in vitro* or *in vivo* (Bouffler *et al*, 2001; Whitehouse and Tawn, 2001; Dugan and Bedford, 2003) and its expression has been reported to depend on the genotype of the irradiated cell/animal (Ponnaiya *et al*, 1997; Watson *et al*, 1997) with considerable inter-individual variation even in those genotypes that may express high levels of instability (Watson *et al*, 2001).

3 There is a consensus that the role of induced instability in radiation cancer risk is not yet clear. For example, the available data are not clear on whether there may be a genomic instability 'footprint' in radiation-associated human cancers (Nakanishi *et al*, 1999, 2001; Lohrer *et al*, 2001; Cox and Edwards, 2002; Little JB, 2002). In general, members believe that it is reasonable to suggest that radiation-induced cancer can arise via directly induced DNA damage and via induced genomic instability. There is at present too little evidence to enable the Committee to judge the balance between these two processes, especially at low doses. Insofar as radiation-induced genomic instability does contribute to cancer risk, it will already be included in the epidemiological observations, but the uncertainties lie in extrapolations to low doses, low dose rates and other exposure scenarios.

3.3 Bystander Effects

4 Bystander effects are known to occur in cells not 'hit' by a radiation track but are in contact with 'hit' cells and/or share growth medium with them (reviewed in Mothersill and Seymour, 2001; Lorimore and Wright, 2003; Morgan, 2003a, 2003b). Bystander effects can be expressed as both induced genomic instability and as DNA damage responses. Reported effects include increases or decreases in damage-inducible and stress-related

proteins, increases or decreases in reactive oxygen and nitrogen species, cell death or cell proliferation, cell differentiation, radio-adaptation, induction of mutations and chromosomal aberrations, and chromosomal instability. Bystander effects have been observed in a variety of experimental cellular systems and there is some evidence that they do not demonstrate a linear relationship to dose. Bystander effects appear to predominate at low doses of radiation, after either low LET X-rays or gamma rays (Seymour and Mothersill, 2000) and low doses of high linear energy alpha particles (Little *et al*, 2002). In some cellular systems, effects are maximally induced by the lowest doses investigated (~10 mGy).

5 There are few data on such effects in whole animals (see, for example, Watson *et al*, 2000; Xue *et al*, 2002) and it is not known whether such effects do or do not influence the cancer process in humans after low doses of radiation. If they do, this could call into question the linear extrapolation from high doses and dose rates to low doses and dose rates. It seems unlikely that bystander effects would be specific to internal radiation or specific to man-made radionuclides. However, some members of the Committee consider that this may not be so for internal radiation from local concentrations of 'warm' radioactive particles deposited in tissues.

6 Views differ on whether bystander effects might increase, decrease or have no influence on cancer risk. Some members believe that for high LET radiations, existing epidemiologically based estimates of risk from alpha particle irradiation include any theoretical impact from bystander effects. Other members remain concerned that epidemiological studies may be insufficiently sensitive to detect the true level of risks especially from very low doses. In their view, there may be increased risks from these novel effects at low levels of radiation, which are undetected or undetectable by present epidemiological studies. There is a consensus that further knowledge about bystander mechanisms and their relationships with the cancer process is necessary to resolve these differences in view. UNSCEAR has recently initiated a review of information on induced genomic instability, bystander effects and their potential implications for radiation risk.

3.4 Minisatellite Mutations

7 'Minisatellite' and related repeat DNA sequences are distributed throughout the genome of mammalian species. In human and mouse germ (ie reproductive) cells, some of these sequences are characterised by very high spontaneous mutation rates, providing the basis for DNA-fingerprint technology. In only isolated cases are minisatellite sequences co-located with functional genes and, therefore, minisatellite mutation has only rarely been associated with recognisable human genetic disease.

8 Evidence for an increased germline mutation rate at two hypervariable microsatellite loci among barn swallows, *Hirundo rustica*, breeding close to Chernobyl has been reported, indicating that mutation events in barn swallows from Chernobyl were two- to ten-fold higher than in birds from control areas in Ukraine and Italy. Also reported was an increased frequency of partial albinism, a morphological aberration associated with a loss of reproductive fitness, but there is no evidence that the two genetic findings are causally related (Ellegren *et al*, 1997). Within the contaminated 30 km zone around the Chernobyl nuclear power plant there is also evidence for rare variants at 13 microsatellite loci in a population of an inbred line of wheat plants, *Triticum aestivum*, grown for one generation. The significance of this is not known and although the spontaneous mutation rate at microsatellite loci in wheat is similar to the spontaneous microsatellite mutation rate in humans the mechanism of radiation-induced germline mutation seems to be different (Kovalchuk *et al*, 2000, 2003).

9 The attention of the Committee was drawn to minisatellites and related DNA sequences because of a series of reports on mutation rates in the offspring of irradiated people in the former Soviet Union (FSU). Additional data from genetic studies with mice

were also considered. The Committee considered these data and the claims that evidence of low dose instability of these DNA sequences posed a major challenge to the current estimates (ICRP, 1991; UNSCEAR, 2000) of risk of heritable disease in the offspring of low dose irradiated humans – particularly in respect of internal radiations. In both human and mouse studies, the reported mutations occurred at too high a frequency to be explained by conventional direct-damage radiation mechanisms of mutation and it has been suggested that they arose from some untargeted process, possibly including genomic instability induced in the germline by radiation exposure. The principal elements of the Committee's work and views are outlined in Annex 3B.

10 The Committee was divided on the robustness of the human data. Some members judged that the FSU data were sufficient to show that radiation can cause a detectable increase in minisatellite mutations in the human germline. Other members were not persuaded and cited evidence of inconsistent results from FSU studies; insufficiencies in some study designs; substantial problems in the estimates of doses received; and, for one study, the failure to adequately validate the mutation assay system used. In addition, the results of genetic studies with the offspring of externally irradiated Japanese A-bomb survivors and of cancer therapy patients were inconsistent with many of the FSU data, in that no excess of mutations was detected.

11 Mouse genetic data reviewed by the Committee showed that these minisatellite-related germline sequences[1] were highly mutable by radiation in absolute terms and that new mutations arose also in subsequent generations. These mouse data clearly pointed towards an unusual mutational mechanism for these sequences and unexpected ongoing transgenerational instability. On the other hand, using the relative measure of doubling dose the radiation mutability of these sequences was similar to that of other genetic endpoints in the mouse.

12 A minority view within the Committee was that the human data did indeed point towards an underestimate, by radiological protection bodies, of the genetic risks of low dose radiation. Some other members, however, expressed the view that, since these hypermutable DNA repeat sequences were only weakly associated with genetic disease in humans and mice, they had little relevance to genetic risk estimates that essentially seek to describe the impact of low dose radiation on the incidence of such diseases in the human population. There was a consensus within the Committee that insufficient information existed to relate quantitatively minisatellite mutation rates in humans to radiation exposures and risks, after either internal or external exposure. The Committee recommended that this matter should remain under active surveillance by those responsible for radiological protection. Overall, the Committee did not arrive at a consensus on this topic.

3.5 Implications for Radiological Protection

13 Radiological protection standards are presently based primarily upon our understanding of radiation risks from epidemiological studies, underpinned by our knowledge of radiation mechanisms (eg double-strand breaks of DNA). Where direct measurements of effect are absent, radiobiology theory of such 'classical' DNA effects has been used to add confidence to our assessment of risk. This is particularly the case with exposures at low doses and dose rates, from internal emitters and external radiation, for which few direct measurements of effect in humans are available. Classical DNA mechanisms of radiation action do not explain the phenomena of radiation-induced genomic instability and bystander effects. It is possible that radiation-induced cancers arise from both induced DNA damage and induced genomic instability. However, at

[1] These sequences exist in all cells but the data, and the Committee's interest, were for the germline.

present, there is insufficient evidence to enable the Committee to judge the balance of effects between the two processes, especially at low doses.

14 Nevertheless it is important that an attempt be made to understand what role these phenomena may have on radiation risks at high and low doses. Although currently most data on radiation-induced genomic instability and radiation-induced bystander effects are from *in vitro* studies, the phenomena have also been demonstrated *in vivo* in rodents (Pampfer and Streffer, 1989; Pils at al, 1999; Watson *et al*, 2000, 2001; Xue *et al*, 2002). Minisatellite instability has been reported in those exposed to radiation from weapons testing in Kazakhstan and in their unexposed children and grandchildren (Dubrova *et al*, 2002a) and in some (Dubrova *et al*, 1997, 2000), but not all (Livshits *et al*, 2001; Kiuru *et al*, 2003), studies after the Chernobyl accident. Minisatellite instability was not observed in the A-bomb survivors (Kodaira *et al*, 1995) nor in radiotherapy patients (May *et al*, 2000). This might provide evidence that exposures to low level, chronic internal radiation could have different consequences from exposures to acute external large radiation doses. Such evidence would be contrary to expectations based on the previously assumed DNA mechanisms but these are now questioned by the existence of radiation-induced genomic instability. However, in this chapter and Annex 3B, considerable uncertainties are noted on the consistency of induction of these phenomena. For this reason some members regard the argument that there is a differential response to internal and external radiation as being rather weak.

15 Overall, radiation-induced genomic instability and bystander effects may be dependent on the genetic makeup of the cell/animal being examined, and indeed that their dose–response relationships at low doses could be linear, supralinear, or sublinear depending upon the host's genetic makeup. With respect to humans, this may raise ethical questions concerning those individuals most susceptible to radiation. This evidence remains very much a matter of discussion within the scientific community. However, if these initial findings were to be confirmed they could provide a biological framework for explaining deviations from conventional expectations for different effects observed at very low levels of radiation. These findings are relevant to both external and internal exposures. The result is that some uncertainty arises as to whether current radiological protection standards adequately protect human health, or conversely, whether they may be too stringent. From what is currently known of radiation-induced genomic instability and bystander effects, current extrapolations of risk may be too high or too low. Several scientists, including authors of research papers reporting laboratory investigations of the phenomena, have drawn attention to the possible implications of their results for radiological protection standards (Hall, 1999; Bridges, 2001; Brenner and Sachs, 2003; Little, 2003).

3.6 Carcinogenic Risks of Particulates

16 The Committee examined the suggestion that spatially non-uniform radiation exposures, from radioactive particulates, may be much more carcinogenic than uniform exposures throughout tissue volumes. It therefore commissioned a literature review of the possible carcinogenic effects of particulate radioactive materials, which has since been published (Charles *et al*, 2003). The review concluded that, on current evidence, the conventional assumption of average dose to a tissue or relevant component should provide a reasonable estimate of carcinogenic risk within a factor of three up or down of the central estimate.

17 A difficulty with the reviewed experimental and epidemiological information was that most of it concerned the carcinogenic risks of 'hot' particles, ie particles with very high radioactivity. The Committee agreed that this information was of some value in addressing the issue of whether particles were more hazardous than the more uniform radiation associated with soluble radionuclides but it was difficult to apply most of this information to lower activity particles more likely to be found in the environment.

18 Data on lung cancer mortality following occupational inhalation of plutonium aerosols, and on the incidence of liver cancer and leukaemia due to Thorotrast administration for clinical diagnoses, did not support a significant risk enhancement factor for particles. Very few animal studies, including mainly lung and skin exposures, provided any indication of a particle enhancement. Some recent *in vitro* malignant transformation experiments provided evidence for an enhanced cell transformation for 'hot' particle exposures but the effect was modest. However, most doses were very high: few studies concerned doses below 100 mGy – the area of interest to the Committee.

19 It appeared from the literature review that there was no convincing evidence from worker, animal or *in vitro* studies that 'hot' particles that delivered high doses to a small surrounding volume of tissue were more hazardous than more uniform irradiation. However, the situation for 'warm' particles that delivered lower doses was less clear due to the paucity of direct observations.

20 Most of the Committee agreed that little information existed which supported enhanced risks from exposures to 'hot' particles, although most studies used relatively high doses. Two members considered that the possibility that 'warm' particles presented a high risk could not be ruled out. The remainder of the Committee remained unconvinced or uncertain of this hypothesis mainly because of the paucity of evidence presented. More detail on the risks and transport of particulates is contained in Annex 2D.

21 The radionuclide ^{90}Sr is of special interest to the Committee as it is a long-lived bone-seeking material. It decays in two steps, first by emitting a beta particle to give ^{90}Y; this is also radioactive and decays to a stable (non-radioactive) isotope by the emission of a beta particle. It is therefore the most important material to be considered in connection with the second event theory (see below).

3.7 Dose Thresholds for Cancer Risk

22 In a series of investigations during the 1980s, Raabe *et al* (1981) administered various quantities of ^{90}Sr to beagle dogs. Doses to the skeletons of these animals were calculated from known deposition patterns, and the incidence of various cancers observed over the lifetimes of the animals. Their incidence was compared with the incidence of cancer in control (non-exposed) dogs. A plot of the results from Raabe *et al*, which the Committee considered, was compatible with a threshold for the incidence of all cancers at about 10 Gy. Below this, there was no increase in cancer incidence in irradiated compared with control animals; above this, the incidence increased in what could be described as a power-law manner.

23 More recently, Tanooka (2001) has reviewed the dose–response in radiation carcinogenesis, particularly after beta irradiation. He defined a non-tumour-inducing dose, D_{nt}, as the highest dose at which no statistically significant increase in the number of tumours was observed. Values of D_{nt} were tabulated for a number of different types of tumours for a wide variety of animals. These values were mostly very small for acute or short-term exposures to X-rays or gamma rays, but at least 10 Gy for electron irradiation. When the exposure was chronic, values of D_{nt} ranged from 5–30 Gy for injected beta emitters. This incorporated the earlier data from Raabe *et al* (1981) and is consistent with them. Such data lead many scientists to conclude that a threshold exists for the induction of cancer by internally deposited beta emitters, a conclusion that appears to contradict the prediction of the second event theory. However, other scientists interpret these data as being consistent with low risks at low doses and a curvilinear dose–response relationship.

24 The possible hazards of alpha emitters such as radium, radon and plutonium have also been examined in some detail. The data for radium have mostly been obtained from direct observations on humans (see Chapter 4). Briefly, these show a threshold at skeletal doses of about 10 Gy. With regard to radon, probably the most comprehensive studies

were those carried out by Gilbert *et al* (1996). These were long and complex, and to summarise them would be difficult. However, one point was clear: evidence of a statistically significant excess of cancer was limited to exposures which corresponded to lung doses of about 0.8 Gy. This value was similar to that found by Sanders *et al* (1993) in their studies with plutonium. More recently, Oghiso and Yamada (2000) reported that the appearance and development of lung tumours in rats exposed to plutonium dioxide occurred in animals that had received a minimum lung dose of 1 Gy. All these values of a minimum dose are close to each other, and again some scientists conclude that a threshold exists for the induction of cancer by internally deposited emitters.

25 However, other scientists argue that there are also animal data, as reviewed by UNSCEAR (2000), that show linear dose–response relationships for cancer induction by alpha-emitting radionuclides over the dose ranges studied. For example, Lloyd *et al* (1993) reported a linear dose–response below 1.3 Gy (average bone dose) for bone cancer induction in dogs given ^{239}Pu intravenously. Similar analyses for dogs given ^{226}Ra also gave a linear dose–response relationship, but with a lower slope, the difference probably being attributable to differences in dose at the bone surface (greater for ^{239}Pu than ^{226}Ra per unit average bone dose; see Chapter 2). Although human exposures to $^{226/228}$Ra (radium dial painters) did not result in bone sarcomas at cumulative average bone doses below 10 Gy, Wick *et al* (1999) have presented data on medical exposures to ^{224}Ra as showing small excesses of bone tumours and leukaemia at average bone doses of about 0.6 Gy, ie below the threshold mentioned in the previous paragraph. Chadwick *et al* (1995) have shown that the radium dial painter data are consistent with a linear-quadratic dose–response relationship and, because of the very low natural incidence of bone sarcoma, this is consistent with very low risk at low doses and dose rates. Nevertheless, recent examination of the pathology of bone tumours suggests that particular tumour types (fibrosarcomas but not osteosarcomas) may only occur at high doses following localised tissue damage (Gössner, 2001).

26 The Committee also briefly examined the evidence that low radiation doses induce beneficial changes in cellular response to radiation and that there are adaptive responses that decrease the sensitivity of cells to subsequent radiation exposure. These responses are observed *in vitro* in some cell systems and *in vivo* in some organisms. There was evidence for such responses in mammalian cells and in mammals but the responses were variable, depended on individual genotype, and were mostly of short duration. It remained unclear whether there may be significant implications for risks from low level internal or external radiation. The topic has been reviewed extensively by UNSCEAR (1994), Pollycove and Feinendegen (2001) and Calabrese and Baldwin (2003): the last cite evidence in support of the existence of hormesis.

3.8 Second Event Theory

27 The second event theory (SET), as proposed by Dr Busby, is that two radiation hits (by electrons or alpha particles) in a cell within a particular time window greatly enhance mutagenic effectiveness and, by implication, cancer risk (Busby 1995; Busby *et al,* 1998; Busby and Scott Cato, 2000). The hypothesis suggests that the cancer risk from specific sequentially decaying radionuclides (such as ^{90}Sr and its daughter ^{90}Y), and from particulate forms of plutonium, has been greatly underestimated.

28 According to Dr Busby, the biological basis of the theory is that the first radiation hit (for example, from the initial beta decay of ^{90}Sr) activates a resting cell in the G_0 phase of the cell cycle and causes it to move into what Dr Busby terms a ‘repair-replication cycle’. A second hit (for example, from the subsequent beta decay of the daughter ^{90}Y) on this cell some hours later when it is in G_2 phase (postulated to be >100 times more radiosensitive) provides for the great enhancement in radiation effects demanded by the theory. Other propositions of the SET, including the Committee’s detailed investigations on the SET, are considered in Annex 3A below.

29 Dr Busby said that standard biological texts supported the view that cells were activated by a first hit of radiation to progress through the cell cycle, and thereby become very radiosensitive to the second hit of radiation. The Committee requested the references to these texts: one (Hall, 2000, page 300) was provided to the Committee. Several members stated that this assertion conflicted with most research literature on the topic for low doses of radiation.

30 The Committee then examined a number of reports which stated that available studies provided little evidence for the proposition that low dose irradiation of quiescent (G_0/G_1) cells triggered progression through the cell cycle (Duncan and Lawrence, 1991; Gadbois *et al*, 1996; Linke *et al*, 1997; Savell *et al*, 2001). On the contrary, much evidence showed that cell cycle checkpoints inhibited cells from progressing through the cell cycle while they repaired DNA damage. Accordingly, the Committee members, apart from two, considered that the available information and data on cell cycling did not support the view that, generally, cell progression was stimulated by low doses of radiation. Instead, checkpoints were likely to be activated and, at higher doses, cell apoptosis (cell suicide) and other modes of cell death were the likely result.

31 Similarly, the available studies provided no indication that the G_2/M phase was consistently characterised by extreme radiosensitivity (Al-Achkar *et al*, 1988; Aghamohammadi and Savage, 1992; Pazzaglia *et al*, 1996). Accordingly the same majority of Committee members also considered that mutational radiosensitivity in the G_2 phase of the cell cycle is usually enhanced by less than a factor of ten (eg Al-Achkar *et al*, 1988; Redpath and Sun, 1990; Chuang and Liber, 1996; Evans *et al*, 1996).

32 The Committee commissioned a literature review by an independent consultant to establish whether experimental support (or otherwise) existed for second event enhancement for cancer-related endpoints, especially from animal experiments in the past that may have inadvertently fulfilled second event criteria. The author of the review concluded that the overwhelming majority of the evidence indicated no such enhancement. Where unexpected effects were seen in a few experiments in the mid-1960s it was debatable whether they may have arisen from second event processes, as their study parameters were insufficiently defined. See Annex 3A for a more detailed discussion of the review.

33 Two members objected to the content of the review and disagreed with its conclusions. In support of the SET, they cited data on unexpected effects from studies by Luning *et al* (1963a, 1963b), Frolen (1970), Nilsson *et al* (1980) and Pohl-Ruling *et al* (1979, 1990, 1991). On the other hand, the other members of the Committee were supportive of the conclusions of the commissioned review. They provided additional data that argued against enhanced cancer risks from $^{90}Sr/^{90}Y$ at low doses: some of these data suggested that there was even a threshold at low doses for some effects. Members pointed out that the more extensive follow-up studies by Frohlen (1970) did not confirm the earlier studies of Luning *et al* (1963a, 1963b), and that a later publication by Luning *et al* (1976) cited Frolen (1970) as the apparently definitive reference in these studies.

34 The view of the Committee, apart from two members, was that the available studies to date offered little or no support to the second event theory as propounded by Dr Busby. Instead, the available evidence substantially contradicted it. The Committee reached this conclusion for the following reasons:

a the lack of biological plausibility for the basic preconditions of the SET;

b the paucity of supporting evidence in the proponents' reviews of the SET;

c the weakness of studies cited in support of the SET; and

d the absence of supporting evidence found by the independent review commissioned by the Committee – see Annex 3A.

3.9 Biphasic (Bimodal) Dose–response Relationships

35 Two Committee members considered that a number of, mainly Russian, studies indicated that the dose–response relationship at low doses and dose rates was biphasic (bimodal) or polymodal in some systems rather than linear (Burlakova *et al*, 1999). If this were the case, exposures to low levels of radiation could lead to higher risks than those predicted by a linear dose–response relationship or predicted from epidemiological studies. Depending on the doses at which the response was greatest, risks could possibly be higher than currently predicted.

36 The other members of the Committee considered that the data presented in the tables in Dr Burlakova's studies were inconclusive as they could be read to indicate linear, biphasic or other responses. The data and their presentation also suffered from substantial shortcomings. For example, the selection of a single average to represent doses in epidemiological cohorts ignored the wide span of doses in each study. In addition, if the underlying response were biphasic, it would not have shown up in the studies, as the response would have been washed out by different individuals in each study having doses spread across the dose scale. Most members were not persuaded of the existence of the phenomenon or of its generality. It seems likely that only further research on biological mechanisms would shed light on whether such a response existed and on the degree to which it were relevant to risks at low doses.

3.10 Artificial versus Natural Radionuclides

37 The Committee considered whether man-made nuclides differed generically in their effectiveness from naturally occurring nuclides. In the view of two members, humans had evolved ways of responding to naturally occurring nuclides, but these (unspecified) mechanisms did not cope with recent man-made nuclides such as ^{90}Sr and ^{137}Cs released, for example, in bomb fallout. The remainder of the Committee did not agree with these views. They considered that, although ^{90}Sr and ^{137}Cs were indeed potentially hazardous nuclides, their effectiveness was recognised in their respective dose coefficients that reflected their tissue uptakes, half-lives and decay energies. This also applied to alpha emissions from both artificial and naturally occurring radionuclides, including ^{222}Rn, ^{226}Ra, ^{239}Pu and ^{239}Np. In addition, many other nuclides were both naturally occurring and man-made, such as ^{40}K, ^{3}H, ^{14}C and ^{35}S.

38 The Committee recognised that, amongst the very broad array of natural and man-made radionuclides, some were more hazardous than others. However, the degree of hazard did not depend on their origin, but on their individual physical, chemical and radiological properties. Of course, these individual properties should be taken fully into account in assessing the risks from intake of each radionuclide. To a large extent, this was already done in the ICRP biokinetic and dosimetric models, but members differed on the extent to which further detailed assessments were required for some specific radionuclides (for example, tritium and Auger emitters) and chemical forms, because of their particular properties and micro-distributions. The Committee unanimously agreed that radionuclides did not differ intrinsically in their effectiveness depending on whether they were man-made or naturally occurring.

3.11 Conclusions

39 The views of the Committee were divided on many interpretational aspects of the biological data considered in Chapter 3. On induced genomic instability, bystander effects, minisatellite mutation induction and specific issues of microdosimetry, there was general agreement that many of the phenomena were real and some may well be an integral part of cellular and tissue response. There was, however, substantial disagreement as to whether the available data were sufficient to draw firm conclusions on the implications for

radiation-induced health effects. A minority of the Committee held the view that the data clearly provided a major challenge to current estimates of low dose health effects and these members emphasised the implications for internal emitters. Other members were less persuaded on the scientific strength of the case. Many of these members believed that considerably more knowledge was needed and some considered that current epidemiological measures of risk were likely to incorporate contributions from these novel cellular responses, albeit with some low dose/low dose rate uncertainties.

40 On the second event theory, 'hot' particle theory, biphasic responses and artificial versus natural radionuclides**,** two members considered that, together, these theories meant that current ICRP risk models were very inaccurate and could underestimate the true level of radiation risks by two to three orders of magnitude or more. About a third of the Committee disagreed with these theories and with the view that the ICRP risk estimates were greatly inaccurate. Another third also disagreed with the above theories, but considered that current radiation risks might still be seriously underestimated, in some cases, though for different reasons. See below and Chapter 2.

41 Almost half of the Committee members were of the view that the biological evidence on these mechanisms (ie see paragraph 39) was not adequately reflected in current ICRP models. Current risks could therefore be underestimated, at least to some degree, and perhaps significantly for some nuclides. These members considered it was possible that these underestimates could account for some epidemiological findings, especially at Seascale where COMARE had concluded that the observed leukaemia incidence would require radiation risks to be about 200- to 300-fold greater than those estimated by the NRPB (COMARE, 1996). These members pointed out that these biological mechanisms could act together (ie be multiplied), rather than separately (ie be added), to enhance risks to levels required to explain observed increases in risks.

42 The remaining members of the Committee were unsure of the implications. Of these, some were inclined to the view that risks were adequately taken into account in current models and epidemiological observations, and some to the view that more evidence was required before significant changes were made in current risk estimates for internal emitters. These differences of view existed because of lack of knowledge, particularly for the effects of low doses of radiation in *in vivo* studies. Members were agreed that long-term research was needed on the implications of these mechanisms for radiation risks, from both internal and external radiation.

43 Although the Committee did not discuss the matter at length, the majority of the Committee did not hold the view that a dose threshold, ie no risk at low doses, was a general feature of radiation cancer risk. Some members agreed, however, that the dose–response for cancer in some tissues was highly curvilinear and in specific circumstances an apparent dose threshold for risk might apply.

44 There was general agreement that new findings on the biological effects of radiation should continue to be included in consideration of health risks at low doses and their quantitative uncertainty. In this respect, the Committee recognised that current recommendations from the ICRP that were formulated in 1990 pre-dated much of the biological information discussed in this chapter. The Committee endorsed ongoing national and international radiobiology research programmes particularly in respect of microdosimetry, induced genomic instability, bystander effects, cancer mechanisms and germline minisatellite mutagenesis.

45 The Committee did not agree on whether the biological evidence discussed in this chapter had immediate implications for radiological protection standards. A minority of the Committee considered that this was so and that Government should give consideration to applying the Precautionary Principle. Other members, whilst generally supportive of a precautionary approach to the interpretation of scientific evidence, did not share this view,

principally because of their perception of a current lack of coherence in the experimental data and absence of clear links with health effects.

46 There was general agreement that whilst much has been learnt from studying the responses of individual cells irradiated *in vitro*, studying isolated cells cannot reveal the complexity of tissue responses in which complex cell–cell interactions and micro-environmental factors contribute to the overall *in vivo* response. Complex tissue responses may be of particular relevance to the effects of certain inhaled or ingested radioactive particles that become non-uniformly distributed in tissue and give rise to local doses which are high compared with the same amount of energy averaged over the whole body or organ. Accordingly, the Committee recommends that research effort be put into whole-tissue radiation responses.

3.12 Specific Recommendation for Biological Research

47 The Committee agreed a set of specific research recommendations to identify whether a large fraction of a given ^{90}Sr intake bound preferentially to chromosomes rather than being distributed relatively uniformly throughout cells or being retained in non-cellular matrices. In order to investigate this, the Committee recommends that the following research be carried out:

a *in situ* determination of ^{90}Sr binding to chromosomes;

b determination of ^{90}Sr in isolated chromatin;

c cytogenetic analysis of ^{90}Sr-induced chromosomal aberrations, in the same human cell culture system as (a) and (b); and

d follow-up of an *in vivo* study carried out in the late 1960s on the effects of low doses from ^{90}Sr on numbers of cells in rat bone marrow (Stokke *et al*, 1968), including a quantitative assay of chromosomal aberration induction.

ANNEX 3A
Biophysical and Biological Aspects of the Second Event Theory

(1) The second event theory (SET) was formulated by Busby (1995, 1996) in order to investigate the possibility that ^{90}Sr and other sequentially decaying radionuclides had unusual biological properties and posed extreme tumorigenic risk. The theory is based on the assumption that the first ^{90}Sr–^{90}Y beta particle decay serves to synchronise hit cells in the G_2 phase of the cell cycle. The G_2 synchronisation process then creates a highly radiosensitive sub-population of cells and a subsequent hit from the second ^{90}Sr–^{90}Y decay series during this time window provides for extremely high mutational and hence tumorigenic response. Busby (1995) proposed also that the theory should apply also to multiple alpha particle decays from plutonium oxide particles.

(2) Figure 7.2 of *Wings of Death* (Busby, 1995) depicts the above theoretical model. The initial calculations in *Wings of Death* were revised following a recognition of the solid angle properties of radionuclide decay. This revision, published on the LLRC website (Busby, 1996), claimed a ~30-fold enhancement for a ^{90}Sr exposure of 1 mGy per year as compared with the same dose/dose rate of external natural background gamma rays. Edwards and Cox (2000) recalculated the second event probabilities in the above scenario and a commentary plus correspondence with Busby was published. The principal conclusions from the published analysis are given below.

(3) The calculation by Busby (1996) was questionable because of computational/ statistical problems associated with cell packing, the contribution from three or more tracks, estimates of the number of events per cell, and the independent order of events. The enhancement value of ^{90}Sr based upon Busby's model was given by Edwards and Cox as ~1.3. Because the model is based upon a two-hit process the cellular dose response would be highly curvilinear for low dose single decay isotopes and would predict an extremely high dose and dose rate effectiveness factor (DDREF) for tumorigenesis whereas the current ICRP judgement for DDREF is only two.

(4) Thus, irrespective of its biological plausibility, according to Edwards and Cox (2000) the second event theory does not predict the extreme tumorigenic properties of ^{90}Sr that Busby had claimed. Its application would, however, lead to a substantial reduction in the low dose tumorigenic risk of radionuclides with single low LET decays.

(5) The Committee deduced that a consequence of the second event hypothesis would be that the biological effectiveness of low doses of external low LET radiation would increase as the square of the dose rate, according to the probability of a random second event coinciding with the radiosensitive window of a previously hit cell. For example, in an area of high natural low LET background radiation (at say 40 mSv per year), the SET would predict a risk 1600 times greater than in an area at 1 mSv per year. The Committee was not aware of any experimental or epidemiological observations to support this dramatic expectation.

(6) The Committee agreed at an early stage that the SET was an uncertain but potentially important element of the judgements it was seeking to make on the risks posed by exposure to sequentially decaying internal radionuclides; the SET might also have implications for the biological effectiveness of particulate forms of radionuclide characterised by multiple decays. Agreement was reached that the Committee's work should focus on:

a an independent recalculation of the SET ^{90}Sr data presented by Edwards and Cox (2000), together with consideration of other potential 'second event' radionuclides;

b an independent review of the biological plausibility of the SET and other relevant radiobiological data;

c trial calculations regarding second event probabilities for alpha-emitting plutonium oxide particles.

Recalculation of SET Probabilities for ^{90}Sr–^{90}Y Decays and Consideration of ^{132}Te–^{132}I Decays

(7) Independent recalculation of second event probabilities for ^{90}Sr–^{90}Y decays based upon perfect packing of cells plus intracellular location of ^{90}Sr gave results very similar to those of Edwards and Cox (2000), ie a modest (<2) enhancement of possible biological effectiveness of ^{90}Sr. Importantly, subsequent discussion led to agreement that the differences between the calculations of Busby (1996) and Edwards and Cox (2000) can be largely ascribed to the use of a cell packing density of only 10% by Busby and his requirement for all ^{90}Sr atoms retained from a given intake to be closely associated with chromosomal DNA. This demand served to substantially enhance second event probability but was judged by some Committee members to be implausible, particularly since there were many data showing non-cellular deposition of ^{90}Sr in bone matrix.

(8) Calculations by the Committee on second event probability for ^{132}Te–^{132}I were made according to Edwards and Cox (2000) and these are presented in Table 3A.1 below together with the original data for ^{90}Sr–^{90}Y.

(9) From these data it may be concluded that second event probability for ^{132}Te is around 3-fold more than that of ^{90}Sr; as compared with annual gamma ray doses from natural background, the biological enhancement factor for ^{132}Te under the SET would therefore be around 1.8 (^{90}Sr ≈ 1.3).

Table 3A.1 Second event probabilities for decay of ^{90}Sr and ^{132}Te

	^{90}Sr–^{90}Y	^{132}Te–^{132}I
Parent nuclide		
Electrons per decay	1.00	1.23
Mean energy per decay	196 keV	103 keV
Half-life	28.8 y	78 h
Daughter nuclide		
Electrons per decay	1.00	1.00
Mean energy	935 keV	489 keV
Half-life	64 h	2.3 h
No. of disintegrations per gram of tissue per 1 mGy	5.52×10^{6}	10.6×10^{6}
No. of cells per gram	1.91×10^{9}	1.91×10^{9}
Fraction with a parent decay	2.9×10^{-3}	5.5×10^{-3}
Fraction 9.5 to 10.5 h apart	9.7×10^{-3}	1.5×10^{-2}
Fraction with a double event	2.8×10^{-5}	8.2×10^{-5}
Correction factor for remote cells	1.1	1.13

Review of the Biological Plausibility of the SET and Other Relevant Radiobiological Data

(10) In order to explore more fully the biological plausibility of the SET, the Committee commissioned an external scientific review on other relevant experimental data from Dr Barrie Lambert. This review considered studies on ^{90}Sr effects in animals and plants, fractionated/low dose rate animal carcinogenesis data, the effects of plutonium on the reproductive system and adaptive responses to radiation. Additional cellular data on the induction of chromosomal aberrations and cell transformation were also reviewed. Data relating to dose rate and dose fractionation effects were included in the review because the Committee judged that under certain conditions of such exposures the theoretical requirements of the SET would be met. The review paper and, subsequently, the Committee paid particular attention to the initial data of Luning, Frolen and co-workers on the genetic effects of ^{90}Sr in mice (Luning *et al*, 1963a, 1963b). These initial data were suggestive of unexpectedly high effectiveness of ^{90}Sr for the induction of dominant lethal mutations which might be taken as evidence for the SET. However, a comprehensive and carefully controlled follow-up study by Frolen *et al* (1970) failed to reproduce this effect – ^{90}Sr was not found to be an effective inducing agent for dominant lethal mutations.

(11) The Lambert review concluded overall that, from the data considered relevant, it is not possible to totally exclude unexpectedly increased radiobiological effects attributable to the SET but that the bulk of evidence tends to argue against this proposition. This conclusion was accepted by most but not all members of the Committee; interpretation of the data of Luning, Frolen and co-workers was a particularly contentious issue. There was, however, agreement that unexpected but unconfirmed findings on the high effectiveness of low dose ^{90}Sr in reducing bone marrow cellularity in rats warranted further investigation.

(12) In these studies, Stokke *et al* (1968) showed reductions in bone marrow cellularity of 10% or greater at estimated doses of 0.1 mGy and above. There were considerable uncertainties in dose estimates and the authors' opinion was that no clear conclusions could be drawn. The Committee considered that follow-up studies of the ability of low dose skeletally deposited ^{90}Sr to induce chromosomal aberrations in bone marrow may be warranted (see research recommendations in Chapter 6).

Calculation of Second Event Probabilities for Plutonium Oxide Particles

(13) The multiple alpha decays from a plutonium oxide particle residing within a mass of cells would be expected to allow for the production of second events in a fraction of cells within alpha particle range (approximately up to the fourth shell of cells). The Committee undertook two independent sets of calculations to determine second event probabilities for plutonium oxide particles of 0.5 μm and 1 μm diameter residing within a single cell, since these were proposed as the most effective particle sizes for the SET. These calculations were based upon the method of Edwards and Cox (2000) and both sets of data provided evidence that second event probability was high – for 0.5 μm diameter particles ~400 of the 500 cells in the irradiation volume would be subject, per year, to a second event within the time window, as a consequence of multiple alpha particle track traversals. In one of the sets of calculations performed by Committee members it was pointed out that the data indicate a strong requirement for multiple alpha track traversals and that this would lead to supra-lethal alpha radiation doses to cells with second events. For a 0.5 μm particle the alpha doses to 'second event cells' ranged between ~34 and ~470 Gy. Since inactivated cells cannot contribute to cancer development many Committee members questioned the relevance of these data to cancer risk; others were less concerned by the magnitude of these local doses from plutonium oxide particles. The tumorigenic properties of 'hot' and 'warm' radioactive particles together with the efficiency of transport of such particles to the developing embryo/fetus were also considered.

Biological Data Relevant to the SET

(14) There was general agreement that biological plausibility was a crucial factor for the SET and that two critical propositions on cellular response were needed to underpin the SET. First, that irradiation of quiescent (G_0/G_1) cells served as a mitotic trigger for progression through the cell cycle. Second, that following entry into the cell cycle, G_0/G_1 irradiated cells were blocked at high frequency (~100%) in the G_2/M phase and that this causes them to be extremely sensitive to the mutagenic effects of a subsequent radiation exposure (the second event). The Committee sought evidence of these responses through a literature review, the outcome of which is summarised below.

Mitotic Activation of G_0/G_1 Cells by Ionising Radiation

(15) A number of well-conducted studies argue against the first proposition. Indeed the most consistent cellular response observed is that irradiation in G_0 or early G_1 leads to initial cell cycle arrest in G_1 not G_2. This arrest can be long-term or even permanent (Linke *et al*, 1997; Savell *et al*, 2001) and there is also evidence that irradiation in G_0 can render cells less responsive to biochemical mitogens that act to drive cells through the cell cycle (Duncan and Lawrence, 1991); this lack of responsiveness is probably associated with G_1 arrest or with the onset of programmed cell death (apoptosis). In some cases these responses have been linked with the activity of particular genes/proteins, eg p53 and p21 (Gadbois *et al*, 1996; Linke *et al*, 1997). Cells that, after an initial delay, escape the G_1 block can also arrest later in the cycle (Gadbois *et al*, 1996). There is also good evidence for high cellular repair capacity in the G_0 phase as judged by post-irradiation holding of cells in the G_0 phase prior to mitogenic stimulation (UNSCEAR, 2000).

(16) Overall, it proved difficult to find any experimental support for the post-irradiation mitogenic stimulation and specific high frequency G_2 arrest that is demanded by the SET. *Wings of Death* (Busby, 1995) which initially describes the theory, appears not to contain specific reference to published research and although some reference was made to statements in early textbooks, the Committee was unable to clarify these. At a very late stage of the Committee's proceedings, Dr Busby referred to work on gene expression cited by Hall (2000) but there was insufficient time to review this area of work.

Extreme Radiosensitivity in G_2 Phase

(17) The SET requires that cells are extremely radiosensitive in G_2 as compared with other cell cycle phases. The published literature suggests that such cell cycle variation is rather modest and that cellular radiosensitivity is not consistently greatest in G_2/M. For mutation induction at the *Tk* locus, human lymphblastoid cell lines were most radiosensitive in late G_1 to mid-S phase; for *HPRT* locus mutation, G_1 phase was most radiosensitive (Chuang and Liber, 1996). In mouse L cells, G_1 and G_2/M phases were most sensitive to mutation induction at the *HPRT* locus in one study (Evans *et al*, 1996); in a second study G_2/M was more specifically sensitive to neutrons but not to gamma rays (Tauchi *et al*, 1993).

(18) For chromosomal aberration induction it is generally accepted that G_2 is a radiosensitive phase of the cell cycle but quantitative interpretation is made difficult because different classes of aberrations are induced in different cell cycle phases. In human lymphocytes the general picture for chromatid damage is that late S and G_2 cells give higher aberration yields than those in early S (Aghamohammadi and Savage, 1992). These differences are not, however, large. Differences in cell cycle radiosensitivity of up to 6-fold were reported in an earlier study (Al-Achkar *et al*, 1988).

(19) Data on the induction of cell transformation were found to be somewhat variable. In one study with C3H 10T1/2 cells the variation in sensitivity through the cell cycle was 3.1-fold for X-rays and 1.4-fold for fission neutrons (Pazzaglia *et al*, 1996). Other studies

with C3H 10T1/2 suggest a two-hour window of sensitivity in G_2 or late S (Miller *et al*, 1992). C3H 10T1/2 cells are highly abnormal and a questionable model for cancer-related changes. The same applied to the HeLa/skin fibroblast hybrid cell model. In this system based upon antigen expression a 10–20-fold higher sensitivity in M and G_2 as compared with mid G_1 was observed at 1 Gy (Redpath and Sun, 1990). However, when cell survival effects were taken into account, transformation frequencies were similar in different cell cycle phases.

(20) The general picture that emerged is that the G_2/M phase of the cell cycle is frequently but not always a notably radiosensitive period. The data on gene mutation are, perhaps, most relevant to the SET. These data suggest a degree of locus specificity but no indication that the G_2/M phase is consistently characterised by extreme radiosensitivity. Chromosomal and *in vitro* transformation studies also tend to argue against extreme and consistently expressed radiosensitivity in G_2/M.

Binding of ^{90}Sr to Cellular DNA

(21) A potentially important question for the SET is whether ^{90}Sr and perhaps other radionuclides bind with high affinity to cellular DNA. A review of the scientific literature revealed isolated examples of potential ^{90}Sr binding to DNA but, overall, the evidence was equivocal with no examples of high affinity effects. For this reason, and because ^{90}Sr is also of wider interest in microdosimetry, the potential for *in vivo* ^{90}Sr binding was recommended as a topic for further investigation (see research recommendations in Chapter 6).

ANNEX 3B
Minisatellite DNA Mutations in Germ Cells

(1) The term 'minisatellite loci' is used commonly to describe sets of tandem repeat DNA sequences distributed throughout the germline genome of mammalian species. In mice such loci are more correctly termed expanded simple tandem repeats (ESTR). At present, minisatellite loci are considered to have no functions, although this is a matter of much interest and discussion.

(2) A general property of these repeat sequence loci is that they tend to be subject to a high spontaneous mutation rate, although some are relatively stable while others are extremely hyper-mutable (Bois, 2003). In only isolated cases are minisatellite sequences co-located with functional genes and, therefore, minisatellite mutation has only rarely been associated with recognisable human genetic disease (Bridges, 2001).

(3) The Committee considered a series of studies of individuals and their children exposed to radiation in the former Soviet Union (FSU) and the suggestion that these may be indicating novel mechanisms of germ cell mutations by radiation. Some of these reports, based on a comparison of the frequencies of mutation of unstable minisatellites in the offspring of low dose exposed and control parents, were suggestive of very high induced mutation frequencies after radiation. These and other data have raised the question of possible health effects from radiation-induced minisatellite mutations (see Bridges, 2001). They have also prompted claims that current judgements of human genetic risk after radiation (eg ICRP, 1991; UNSCEAR, 2000) are gross underestimates.

(4) The Committee reviewed these and other human/mouse genetic data and its views may be summarised as follows.

Human Data

a Some FSU studies indicate positive results (Dubrova *et al*, 1996, 1997, 2002a, 2002b), while others are equivocal or negative (Livshits *et al*, 2001; Kiuru *et al*, 2003).

b No consistent pattern of response is evident (ie of human germline minisatellite mutations to low dose ionising radiation). This does not mean there is no effect, merely that we are at an early stage of understanding it. If radiation does induce a detectable increase in minisatellite mutations in human studies of the above type, the very high induced mutation frequencies would imply a novel mechanism of radiation mutagenesis (Bridges, 2001).

c Earlier FSU studies contain uncertainties in the adequacy of control populations and in their dose estimates, including the relative contributions of internal and external radiation to germ cell dose (Neel, 1999*).*

d Follow-up studies of the offspring of parents exposed to external radiation from the A-bomb explosions in Japan (Kodaira *et al*, 1995) and from medical irradiation (May *et al*, 2000) reveal no observable excess of minisatellite mutations.

Mouse Data

a Mouse genetic studies with unstable ESTR loci provide clear evidence of a mutational dose–response after external radiation by X-rays, gamma rays and neutrons (Fan *et al*, 1995; Dubrova *et al*, 1993, 1998, 2000a). (As yet, there are no mouse data following exposures to internal emitters.)

b The very high absolute frequencies of radiation-induced mutations also seen in mouse data support the idea of a novel mutational mechanism for unstable ESTR loci involving untargeted radiation damage. That is, mutations are induced without the obvious need for a direct ionisation 'hit' from an electron track (Bridges, 2001).

c Mouse studies have shown also an increased frequency of new mutations arising in the germline of the F_1 offspring of irradiated mice. This might imply some ongoing increase in genomic instability through the germline as the result of the parental irradiation (Dubrova and Plumb, 2002). On the other hand, using the relative measure of mutation doubling dose (DD), the DD of ~0.4 Gy for ESTR mutations is similar to that of other genetic endpoints in the mouse (UNSCEAR, 1994, 2000).

(5) The molecular mechanisms of minisatellite mutations were also discussed, including possible explanations for the very high frequencies of induction by radiation in mice, and possibly humans, and the transgenerational effects in mice (Dubrova and Plumb, 2002).

(6) The Committee also considered an FSU study of other putative DNA locus mutations induced in low dose exposed parents (Weinberg *et al*, 2001). This study claimed that induced germline mutation rates after low doses were remarkably high. Methodological aspects of the study have been questioned (Jeffreys and Dubrova, 2001) including the lack of validation of the mutations scored. Despite correspondence with the research team, the Committee was unable to clarify this matter.

(7) The molecular mechanisms of minisatellite mutations were also discussed and important findings considered to be that spontaneous germline mutations in minisatellites appear to be initiated by double-strand breaks and may involve either inter-allelic rearrangements (gene conversion events) or intra-allelic rearrangements that do not involve exchange of flanking sequences (Jeffries *et al*, 1994). By contrast, somatic instability of minisatellites appears to occur via replication slippage or intra-allelic unequal crossing over (Jeffreys and Neumann, 1997).

(8) In addition to parental exposure to ionising radiation increasing the frequency of germline instability in first-generation (F_1) offspring mice, levels of spontaneous mutation rates and transgenerational instability varied between strains indicating underlying differences in genetic susceptibility. Breeding from unexposed male or female progeny of exposed mice revealed that germline mutation rates in F_2 animals were elevated (Dubrova *et al*, 2000a; Barber *et al*, 2002). These data are not considered to be consistent with the hypothesis of direct targeting of any specific gene(s) in the F_0 male causing destabilisation of the F_1 and F_2 germlines and point in the direction of an epigenetic instability mechanism such as might be attributed to DNA methylation changes.

(9) A study of germline mutations in minisatellites among the inhabitants of regions of Ukraine which were heavily contaminated by radionuclides after the Chernobyl accident has been reported (Dubrova *et al*, 2002b). The control group was composed of 98 children conceived before the Chernobyl accident and born between 1976 and 1986. The exposed group contained 240 children conceived after the Chernobyl accident and born between 1987 and 1996. The families were matched by ethnicity, maternal age, parental occupation, and smoking habits. A statistically significant 1.6-fold increase in mutation rate was found in the children of exposed fathers. This increase in the mutation rate was found in the area, regardless of the year of birth of the children from 1986 to 1995, and suggests that the cumulative parental dose is not relevant for the induction of minisatellite mutation. The authors consider that the initial acute exposure was responsible for the increase and since spontaneous minisatellite mutation in humans occurs mainly by meiotic recombination, the effect is attributable to an induced instability resulting in later destabilisation of minisatellites

during meiosis which persists from the time of the accident until 1995. However, in another FSU study (Dubrova *et al*, 2002b) the mutation rate for minisatellite loci decreased with post-irradiation year of birth, implying that transgenerational destabilisation of these loci is not a consistently expressed effect.

Current Estimates of Human Genetic Risks from Radiation

(10) In general, the Committee recognised that, although there was considerable scientific interest in minisatellite/ESTR germline mutation rates and their underlying mechanisms, quantitative interpretation of the data was difficult because of conflicting findings, dosimetric uncertainties and methodological problems. Nevertheless attention was given to how these data might, in principle, impact on the methods used internationally (ICRP, 1991; UNSCEAR, 1994, 2000) to provide estimates of human genetic risk. In simple terms these methods use a combination of data on human genetic diseases and human/mouse data on gene/chromosomal mutation rates to estimate the responsiveness to radiation of the frequency of genetic disease in the population. By definition, this demands consideration of functional gene/chromosomal mutations rather than of non-functional mutations in DNA repeat sequences, such as minisatellite/ESTR loci, which have only a weak association with genetic disease. On this basis alone, the minisatellite/ESTR studies considered by the Committee are judged by many to be of limited relevance to the estimation of human genetic risk.

(11) The members of the Committee were not unanimous in their views on the above issues but all recognised that there were uncertainties on current estimates of risk of heritable effects. These uncertainties have recently been discussed in detail by UNSCEAR (2000). Heading the list of problems for genetic risk estimation is the failure to find any clear epidemiological evidence of excess genetic disease in the offspring of radiation-exposed parents in spite of extensive study of A-bomb and medically-exposed populations. Some members cited papers published in Russian journals claiming evidence of post-Chernobyl increases in human genetic disorders, usually those of the multifactorial type (Bandazhevsky and Lelevich, 1995; Bandazhevsky, 1997,1998). Others referred to the UNSCEAR (2000) review of post-Chernobyl data that had concluded that such genetic effects had not been convincingly demonstrated.

(12) Further to this, those few genetic disorders potentially associated with minisatellite mutation are of the multifactorial type; such diseases are strongly dependent on environmental factors for their manifestation. Current evidence and analyses (UNSCEAR, 2000) suggest that the frequency of multifactorial diseases in the population will be only weakly related to an increase in mutation rate following radiation exposure.

4 Epidemiological Evidence

4.1 Introduction

1 Epidemiological studies provide the principal basis for quantifying the risks of radiation-induced cancer in humans, and are a major tool in the investigation of other radiation-induced adverse health effects (eg congenital abnormalities and later-expressing genetic diseases). Epidemiology is the scientific study of the distribution and putative causes of diseases in human populations. It may be conveniently divided into descriptive epidemiology and analytical epidemiology. Descriptive epidemiology involves obtaining and presenting appropriate, often routinely collected, data concerning the distribution of diseases in terms of factors such as age, sex, race, occupation, calendar period and geographical location, and it is not concerned with investigating causal or other hypotheses. Analytical epidemiology deals with the investigation of hypothesised causal relationships through appropriate studies such as cohort and case–control studies.

2 Epidemiology is mainly an observational (ie non-experimental) science that draws its data from the uncontrolled conditions of everyday life in which the investigator has no say over which individuals are exposed to which conditions at what levels. As such, even greater care must be taken in designing an epidemiological study, and in interpreting epidemiological results, than in the experimental sciences (eg randomised controlled clinical trials, where the investigator determines which individuals will be given which treatments). This is because of the possible presence of systematic (ie non-random) differences in disease rates in the people with different exposures which are not causally related to the exposure. Bias can enter into an epidemiological study in a number of ways (eg through better ascertainment of cases among the 'exposed' group as compared to the 'unexposed' control group) as can confounding (ie the distortion of the apparent effect of an exposure due to association between that exposure and other factors that can influence the outcome under study). Not only must statistical uncertainties be properly accounted for in epidemiological findings, but the influence of bias and confounding must also be borne in mind when assessing findings because these can distort results to such an extent that they become meaningless.

3 For this reason, interpretational frameworks have been developed – such as the guidelines proposed by Sir Austin Bradford Hill (1965) – to assist in the evaluation of epidemiological associations in order to help distinguish cause-and-effect relationships from non-causal associations. As Bradford Hill put it, the question should always be in our minds as to whether a statistical association produced by an epidemiological study might have an explanation other than cause-and-effect. His guidelines are an aid to providing a reasoned answer to this question and are reproduced in Annex 4D to this chapter.

4 The above considerations mean that epidemiological studies should be designed and interpreted with care. Special attention should be paid, for example, to the following:

a the study variables (eg time periods, geographical areas, illnesses, age ranges, incidence or mortality, latency periods);

b clarity and precision as to the hypothesis(es) to be tested;

c the appropriateness of the chosen methodology, eg whether a concentric circle approach is suitable in a particular geographical correlation ('ecological') study;

d the possibility of undiscovered biases and confounders in a study, eg that exposed individuals differ from unexposed individuals in their experience of background risk factors, as in the 'healthy worker effect';

e selectivity in the presentation of findings or in the publication of a study;

f the presentation of confidence intervals (see Annex 4E);

g consideration of the statistical power of a study (see Annex 4F); and

h the possibility that the dose and risk relationship might not follow a simple monotonic trend.

5 Epidemiology is heavily dependent upon a disciplined approach to the collection, collation and statistical analysis of data, without which reliable findings will not be generated. It is important to distinguish between those statistical associations that will inevitably occur simply as a result of random variation when large numbers of comparisons are made and those that are produced in analytical studies where a specific hypothesis has been specified in advance. From time to time blind chance will inevitably generate unusual and noteworthy findings that do not reflect an underlying raised risk. This is why the rigorous methods of epidemiology have been developed to reduce the chance of 'false positive' results. It is all too easy to imagine particular patterns in data where in fact none exists. Misleading interpretations can easily be made when hypotheses are specified *post hoc* (ie after the investigator has seen the data). An illustration of this is the so-called 'Texas sharp-shooter effect' where the sharpshooter first empties his gun at the barn door and *then* suitably draws the best target around the bullet holes. In this manner, 'clusters' of cases seem to be observed that are no more than random fluctuations picked out for special attention after viewing the data. This is considered further in Annex 4E.

6 A further issue is that the statistical power of a study must be taken into account when evaluating epidemiological data. Low statistical power can lead to 'false negative' results, that is, no association seems to be shown when in fact one exists. Wide confidence intervals that encompass 'no effect' (ie statistically non-significant results) should not be over-interpreted: 'absence of evidence' is not synonymous with 'evidence of absence'. Low statistical power is a particular problem in studies of low level radiation exposure where small excess risks are involved, and any 'signal' indicating a genuine effect could easily be lost in the background statistical 'noise'. Findings from studies with low statistical power are usually compatible with a wide range of magnitude of effect: from risks that are greater than predicted by standard models to beneficial health effects ('hormesis'). This matter is considered further in Annex 4F.

7 It will be seen that considerable care needs to be expended both in constructing epidemiological studies and in interpreting their findings. Only through a broadly consistent and coherent set of results arising from different studies carried out under differing circumstances can reasonable confidence be placed upon a causal explanation of a given association. The danger of over-interpreting isolated findings has to be emphasised, and it is worthwhile quoting the 1994 UNSCEAR report:

> "Studies of disease in human populations must adhere strictly to epidemiological principles in order to achieve valid quantitative results. These include sound case ascertainment, an appropriate comparison group, sufficient follow-up, an accounting for confounding factors and well-characterised dosimetry."

8 Nonetheless, despite the interpretational problems of observational investigations, epidemiological results are obtained directly from the study of groups of humans, and so do not require the inter-species generalisation to humans that is needed in the interpretation of the results from the experimental study of laboratory animals. Nor do epidemiological findings directly depend upon the interpretation of underlying biological mechanisms as determined by *in vitro* experiments, because epidemiology involves the study of clinically overt diseases in humans and therefore implicitly incorporates these

radiobiological processes in its data. However, as noted below, when small excess relative risks are involved mechanistic knowledge can be a valuable guide in the generation of risk models from epidemiological data.

9 The Committee has kept these fundamental aspects of epidemiology in mind when assessing the epidemiological evidence concerning the risks to health of exposure to internally deposited radioactive material. In particular, the Committee appreciates that epidemiological studies of low level radiation exposure can only have limited power and only produce results of limited precision, although findings can provide an envelope of values with which to bound risk estimates. Estimates of risk within this envelope have to be guided by radiobiological knowledge of underlying mechanisms.

4.2 Possible Dose–response Relationships

10 The issue of low statistical power is especially pertinent to the shape of the dose–response curve at low doses. 'Dose–response' is shorthand for the manner in which the magnitude of the specific effect induced by exposure to radiation (eg cancer) varies with the quantity of radiation absorbed by tissue, the dose. For stochastic effects (cancer and hereditary disorders), the dose–response curve is reasonably well defined at moderate to high doses, displaying a steady rise of risk with dose before the risk falls due to cell-killing at high doses. The shape of the dose–response relationship at low doses can be interpreted in different ways for various clinical endpoints, the most widely accepted curve for stochastic effects being the linear no-threshold (LNT) one. This, as the name implies, means that the incidence of the response increases in direct proportion to the dose over the low dose range, there being no threshold below which the effect does not occur. The LNT formulation at low doses is the one favoured by the ICRP but is, however, disputed by some members of the Committee. Various possible dose–response relationships are illustrated in Figure 2.1 of Chapter 2.

11 The Committee recognised that epidemiological data relating to low levels of exposure are compatible with a range of curves describing the variation of the underlying risk with the level of exposure, including a curve that is steeper than the LNT relationship (a 'supralinear' curve), no risk below a certain level ('threshold'), or even a protective effect ('radiation hormesis'). The Committee was divided as to which type of dose–response was considered to be the most convincing description of the available scientific evidence. The member of the Committee who believed most strongly in the existence of a threshold and/or hormesis based his conclusion upon mechanistic arguments and his interpretation of the results obtained from several epidemiological studies (Rowland, 1994; Thomas, 1994; Voelz *et al,* 1997; Ghiassi-nejad *et al*, 2002; Calabrese and Baldwin, 2003; Cameron, 2003). However, most of the Committee considered that the epidemiological evidence for radiation hormesis or a threshold as the preferred risk model was not persuasive.

12 Several members of the Committee were concerned that the term 'dose–response' might be misleading because of the limitations of the meaningfulness of the concept of 'dose' at very low exposures. In such circumstances, it becomes necessary to consider the distributions of the separate radiation tracks ('microdosimetry'). This is considered in Annex 2A of Chapter 2. The epidemiological evidence as a whole needs to be examined in conjunction with recent radiobiological evidence that indicates that a complex dose–response may be possible at low doses, which potentially includes supralinear, threshold or hormetic curves, as discussed in Chapter 3.

13 Two members of the Committee were of the view that the epidemiological evidence supports a biphasic (bimodal) dose–response – a form of supralinear curve in which the dose–response rises steeply at very low doses and then falls before gradually rising again – and point to the work of Burlakova *et al* (1999) on this subject. The other members

judged that this evidence was very weak and did not, by itself, imply a complex dose–response of this nature.

4.3 Radon, Radium and Thorotrast

14 The Committee recognises the considerable effort that has been expended on the epidemiological study of those groups exposed to radon and its decay products, to various radioisotopes of radium, and to the medical contrast medium Thorotrast containing radioactive ^{232}Th (UNSCEAR, 1994, 2000). These are important sources of information on the risk of radiation-induced cancer from internally deposited radionuclides, and findings have recently been summarised by two members of the Committee (Harrison and Muirhead, 2003).

15 In particular, the Committee is fully aware of the predominant role of the inhalation of the naturally occurring radioactive gas radon and its decay products in the radiation exposure of the world population. A number of authoritative bodies have recently comprehensively evaluated the risk to health of exposure to radon and its radioactive progeny, including UNSCEAR (2000) and the BEIR VI Committee of the US National Research Council (NRC, 1999). In addition, COMARE is keeping this matter under review and the NRPB Advisory Group on Ionising Radiation (AGIR) is also currently reviewing radon exposures and risks in the UK. AGIR is expected to publish its report in 2005. The Committee considered there was little it could usefully add to these comprehensive examinations, especially in view of its own heavy work programme. It received numerous representations from one member of the public, which it considered in some detail before replying. These representations did not alter the Committee's view that sufficiently detailed reviews of this subject were already underway.

16 In a similar vein, the Committee did not feel that sufficient disagreement existed among members to spend significant time on discussing in any detail many of the other studies concerning internally deposited radionuclides. These studies have recently been reviewed by UNSCEAR in its 2000 report and by IARC in a report concerning internal emitters published in 2001. As a consequence, the Committee has not made a detailed examination of the effects in epidemiological studies of radionuclides such as ^{32}P or ^{131}I. Instead, the Committee has concentrated upon epidemiological studies relating to radionuclides for which the risks of exposure have been suggested by certain members to be seriously underestimated by standard models. These studies have been identified as key studies by Dr Busby in two papers presented to the Committee in the early stages of the CERRIE process.

4.4 Exposure to Radioactive Fallout

4.4.1 After Chernobyl

17 The accident at the Chernobyl nuclear power plant in Ukraine in April 1986 resulted in a very large inventory of radionuclides being ejected into the atmosphere over a period of ten days. These radionuclides were subsequently deposited in widely ranging concentrations over many countries mostly via washout through rainfall (UNSCEAR, 2000).

18 The Committee considered epidemiological evidence concerning exposure to radioactive fallout from the Chernobyl accident. The Committee concentrated particularly on infant and childhood leukaemia, as two members had asserted that studies of Chernobyl fallout provided evidence that internal radiation risks are being greatly underestimated. Infant leukaemia (ie leukaemia arising within the first year of life) is a very rare disease and is believed to have a different biological origin to that of childhood leukaemia (ie arising after the age of one year) (Greaves, 1997). Consequently, infant leukaemia and childhood leukaemia have been considered separately.

Infant Leukaemia

Mainland Europe

19 Birth cohort studies in Greece, the former West Germany and Belarus have all shown an increased incidence rate of infant leukaemia in the period immediately after the Chernobyl accident, and some of these increases are statistically significant. In Greece, the incidence rate of leukaemia in infants born in the 18 months between July 1986 and December 1987 was raised by a factor of 2.6 (95% confidence interval, CI, 1.4, 5.1) when compared with the rate among infants born outside this period, and a statistically significant trend was observed across three areas of increasing level of contamination (Petridou *et al*, 1996). These authors suggested that the results of their study provided evidence that exposure *in utero* to radionuclides from the Chernobyl accident detectably increased the risk of infant leukaemia. In West Germany, a similarly designed study found a 1.5-fold increase (95% CI 1.0, 2.2) in infant leukaemia incidence for births during these 18 months, although the highest rate was found in the area of lowest contamination (Steiner *et al*, 1998). In Belarus, the infant leukaemia incidence rate during this period was raised 1.3-fold (95% CI 0.8, 2.1) for the whole country, and 1.5-fold (95% CI 0.6, 3.6) for the two most contaminated regions (Ivanov *et al*, 1998). The authors of the Belarusian study caution that it is difficult to interpret these results because of the high reported background rate of infant leukaemia in those not exposed to radiation from Chernobyl. Some members of the Committee questioned the accuracy of the Belarusian data, which were collected at a time of transition in the FSU.

20 For some years, IARC has been co-ordinating the European Childhood Leukaemia/ Lymphoma Incidence Study (ECLIS), covering 36 cancer registries in 23 countries in Europe assessed to possess accurate childhood leukaemia registration data. The most recent report from this study (Parkin *et al*, 1996) presented some separate data for infant leukaemia, which showed 13 cases observed against 7.3 expected in the highest dose category (≥0.30 mSv), but no significant trend of excess incidence with increasing dose. ECLIS was criticised by two Committee members for pooling data from different regions to generate dose groups covering the whole study area; they considered the data from some countries to be unreliable, as the accuracy of some ECLIS data had been questioned (Hoffmann, 2002). However, most other members considered that this was an appropriate methodology as it maximised statistical power. It is of interest that, although incidence data from West Germany and Belarus were included in ECLIS, data from Greece were not, which may indicate some doubts on the part of IARC over the accuracy of the Greek registration data for the 1980s.

21 An updated report from ECLIS dealing specifically with infant leukaemia has been expected for some time and is understood to be due for publication shortly. The Committee recommends that, when published, the updated report should be studied carefully to ascertain what evidence there might be for an elevated risk of infant leukaemia arising from Chernobyl exposures.

United States of America

22 Mangano (1997) examined registrations of infant leukaemia among those born in certain parts of the USA during 1986 and 1987, and found a 30% increase above the expected rate, although this was not statistically significant ($p<0.09$). In interpreting this result it should be borne in mind that the deposition of radionuclides from Chernobyl was very much lower in the USA than in most of Europe (Broadway *et al*, 1988).

Great Britain

23 Gibson *et al* (1998) reported a significant excess of infant leukaemia registrations in Scotland during 1987, which persisted into the first half of 1988. Although no cases of infant leukaemia occurred in Wales in 1987, the four cases diagnosed during 1988 represent an excess over expectation (Busby and Scott Cato, 2000). However, the claim

of Busby and Scott Cato (2000) that three cases were diagnosed in Wales during the first six months of 1988 has been challenged by the Welsh Cancer Intelligence and Surveillance Unit, which maintains that only one case occurred during the first half of the year (Wakeford, 2002). The Scottish and Welsh studies examined incidence by year of diagnosis rather than year of birth, and did not contain information relating the geographical distribution of cases to contamination levels.

24 In order to increase the information available from the incidence of infant leukaemia in Great Britain after the Chernobyl accident, the Committee requested the Childhood Cancer Research Group (CCRG) to collate infant leukaemia registration data for regions of Scotland, Wales and England for the relevant periods. The data are for periods before, immediately after and some time after Chernobyl, and for regions with low, intermediate and high levels of contamination. The Committee conducted its own analysis of these data, based upon an agreed protocol. The pattern of incidence rates for these periods and areas was in the direction expected if Chernobyl contamination had increased the risk of infant leukaemia, but the data were too sparse to allow firm conclusions to be drawn, the results being compatible with no increased risk or even a beneficial effect. For example, adopting the periods of birth used in the Greek, West German and Belarusian cohort studies described above produces an incidence rate for births in Great Britain during July 1986 to December 1987 which is greater than the rate for the combined adjacent periods of birth by a factor 1.22 (95% CI 0.86, 1.69). In absolute terms, this corresponds to an estimated 6.7 (95% CI –4.5, 19.7) additional cases per million births during the 18-month period after Chernobyl. Thus, the British infant leukaemia data cannot determine whether the standard risk coefficient is inaccurate. The Committee commends to COMARE its documents on this study as an example of how differences in analysis, conclusions and interpretation can arise amongst individuals even when they start with identical data and agreed hypotheses to test.

Summary

25 Overall, the findings of studies examining the incidence of infant leukaemia after the Chernobyl accident do not provide sufficiently persuasive evidence that the risk of internal exposure to radionuclides is seriously underestimated by risk estimates obtained from studies of exposure *in utero* to sources of external irradiation. The only study to show a large discrepancy with the predictions of external radiation risk estimates is the Greek birth cohort study of Petridou *et al* (1996); but the risk coefficient that may be derived from the results of this Greek study is statistically inconsistent with that obtained from the findings of the study in Belarus (Ivanov *et al*, 1998) where the highest doses from Chernobyl contamination were received. Consequently, no firm conclusions can be drawn from the infant leukaemia studies, although further results from other studies – especially the completion of ECLIS for infant leukaemia – would be desirable.

26 In the judgement of a large majority of Committee members, it is likely that radioactive fallout from the Chernobyl accident resulted in an increased risk of infant leukaemia in the exposed populations. A substantial fraction of members thinks that this increase is at the level anticipated from current risk models. However, another substantial fraction feels that these models may have underestimated the level of this increased risk. Of this latter group, two members further believe that the evidence for infant leukaemia suggests that the current risk estimates are appreciably in error. The remainder of the Committee believes that there exists relatively little evidence that lends support to this view. There is a consensus within the Committee that leukaemia incidence in infants post-Chernobyl merits further study.

Childhood Leukaemia

27 A significantly raised incidence rate of leukaemia among children under ten years of age who were born in 1986 in a heavily contaminated region of Ukraine, when compared

to the rate in children born in a lightly contaminated region, was reported by Noshchenko *et al* (2001). A subsequent case–control study (Noshchenko *et al*, 2002) of leukaemia among residents aged 0–20 years at the time of the Chernobyl accident in the two most contaminated regions of Ukraine found a significant association with assessed dose, which was strongest for acute leukaemia in those exposed as young children. However, only just over one-third (98) of ascertained leukaemia cases were included in this study and the authors urge caution in the interpretation of their findings. No variation in childhood leukaemia incidence rate with level of contamination was found in the different regions of Belarus (Gapanovich *et al*, 2001). Nor were significant excesses of childhood leukaemia incidence found in moderately-contaminated Sweden (Hjalmars *et al*, 1994; Tondel *et al*, 1996) and Finland (Auvinen *et al*, 1994).

28 ECLIS examined childhood leukaemia incidence across Europe during 1980–1991 (Parkin *et al*, 1996). There was a slight increase in incidence in Europe during these 12 years, but the geographical distribution of this increase, the start of which pre-dates the Chernobyl accident, bears no relation to the level of contamination from the Chernobyl accident. In particular, when split by the estimated dose due to the Chernobyl accident, the ratio of the observed number of cases in the 0–14 year age group to the number of cases expected in the absence of a radiation effect was very close to 1 in each dose group. Some doubts have been expressed about the accuracy of case ascertainment and dose assessment (Hoffmann, 2002), although it is unclear what effect these might have on the results. Thus, there is no indication from this study that the risk of childhood leukaemia from exposure to radionuclides released from Chernobyl has been seriously underestimated.

29 In contrast to the findings of the birth cohort studies conducted in Greece (Petridou *et al*, 1996), West Germany (Steiner *et al*, 1998) and Belarus (Ivanov *et al*, 1998) of raised levels in the incidence of infant leukaemia among births during July 1986 to December 1987 (as discussed in paragraph 19 above), these studies provide little indication of an excess of leukaemia incidence among young children aged 1–3 or 1–4 years born during this period. Hence, any underestimation of the excess risk of infant leukaemia that might exist among those born immediately after the Chernobyl accident does not appear to persist into the later years of childhood.

30 A large majority of the Committee believes that the epidemiological evidence does not provide a sufficient basis to conclude that the risk of childhood leukaemia beyond the age of one year from exposure to radioactive contamination from the Chernobyl accident is substantially underestimated by current risk estimates. Two members maintain that studies do show that such an underestimation exists.

Childhood Thyroid Cancer

31 The Committee accepts that the evidence for a substantial excess risk of thyroid cancer among children resident in the heavily contaminated regions of the FSU at the time of the Chernobyl accident (UNSCEAR, 2000) is overwhelming. Members also recognise the considerable uncertainties involved in the derivation of a risk coefficient from these data because, for example, of difficulties in accurately assessing thyroid doses. Nonetheless, childhood thyroid cancer risk estimates derived from the Chernobyl data are not greatly at variance with risk estimates obtained from groups of children exposed to external sources of radiation for therapy purposes (Ron *et al*, 1995).

Other Cancers

32 Two members of the Committee were of the view that there is clear evidence of excesses of childhood cancers other than leukaemia and thyroid cancer, and of adult cancers, after the Chernobyl accident, which is related to the resultant contamination.

However, other members felt that this evidence, which has been comprehensively reviewed in the UNSCEAR 2000 report, is not persuasive (see, for example, Moysich *et al*, 2002).

4.4.2 Exposures from Atmospheric Nuclear Weapons Testing

33 Fallout from atmospheric nuclear weapons testing exposed people globally – although to a greater extent in the Northern Hemisphere, where most of the explosions took place, than in the Southern Hemisphere – to radionuclides such as ^{137}Cs, ^{90}Sr and ^{239}Pu. Those living close to testing sites (such as the Nevada Test Site in the USA and Semipalatinsk in Kazakhstan) will have been particularly exposed. Atmospheric testing commenced in the mid-1940s and increased in frequency towards the end of the 1950s and especially in the early 1960s in the run up to the test ban treaty of 1963 (UNSCEAR, 2000). As with contamination from the Chernobyl nuclear reactor accident, it has been suggested that the risk arising from exposure to radionuclides in weapons testing fallout has been greatly underestimated. The evidence for such a serious error has been examined by the Committee. Of special interest is childhood leukaemia because of its enhanced sensitivity to induction by radiation and the short lag-time between exposure and the manifestation of the excess risk. However, incidence data for this period are preferable to mortality data because of the increasing success of treating childhood leukaemia, which was almost invariably fatal before 1960. This led to decreases in childhood leukaemia mortality rates in developed countries after 1960, which were not reflected in decreasing incidence rates. This complicates studies because accurate cancer registration data for this period were only available from a few countries.

United States of America

34 Archer (1987) examined leukaemia deaths in US children and teenagers (5–19 years of age) between 1949 and 1979, and found higher rates in the periods and places where exposures from nuclear weapons testing were higher. Radiation risks derived by his study were similar to those predicted by the current risk models. Regional differences in leukaemia rates corresponded to a composite exposure index that used ^{90}Sr concentrations in food, cow's milk and human bone. Some members concluded that this study implied increased risks from internal exposures to ^{90}Sr that are greater than predicted from standard risk estimates. One major problem with the Archer study was that it was a study of mortality, so that patterns that might be related to exposure to fallout have to be detected against a changing background rate, which may not have changed at a constant rate in all areas. This makes Archer's findings difficult to interpret.

35 In a case–control study, Stevens *et al* (1990) investigated 1177 people who had died from leukaemia and 5330 people (as matched controls) who had died from other causes in southwest Utah between 1952 and 1981. A comprehensive assessment was made of the dose received by the red bone marrow of each study subject from fallout from the Nevada Test Site, and of the associated dose uncertainties. They found a statistical association between leukaemia mortality and fallout dose, which was strongest for acute leukaemia among young people in the earlier years of the study period: for deaths from acute leukaemia during 1952–1963 while under 20 years of age, the relative risk for the group receiving a dose ≥6 mGy was 7.82 (95% CI 1.90, 32.2) based on five cases. Stevens *et al* (1990) concluded that the excess leukaemia deaths, especially those among young people, were attributable to weapons testing fallout. Given the assessed individual radiation doses, the observed number of excess leukaemia deaths was compatible with the number predicted by standard models based principally upon high external dose studies. Although this is a study of leukaemia mortality rather than incidence, this well-designed, individual-based study produces reliable results; it is the only study of weapons testing fallout and childhood leukaemia that takes into account individual factors such as radiation dose.

Nordic Countries

36 The Nordic countries have maintained high quality national cancer registries for a period that stretches back to the time of peak atmospheric nuclear weapons testing. Darby *et al* (1992) examined temporal trends in childhood leukaemia incidence in the combined five Nordic countries in relation to radiation exposures from weapons testing fallout: (a) of children after birth, (b) of the fetus *in utero*, and (c) of paternal testes. Rates of leukaemia incidence were significantly raised in the high exposure period relative to the adjacent medium exposure periods: an excess relative risk of 0.07 (95% CI 0.00, 0.14) for children under the age of 15 years and an excess relative risk of 0.11 (95% CI 0.00, 0.24) for young children under the age of 5 years. Although these excess relative risks are statistically significant, the magnitude of the excesses is small. They are compatible with the risks predicted by standard radiation risk models, although they would also be compatible with somewhat larger risks.

37 The Committee discussed this study in some detail as it was often quoted in support of standard risk estimates and two members suggested that it was seriously flawed. The uncertainties in the risk estimates derived from the study were probably within a factor of five either way of current risk estimates, that is, within the range of uncertainties of standard risk estimates. A number of queries were raised by some members concerning the data used in the study. Therefore, experts in Nordic countries were contacted for their views on the quality of the data, and they supported the accuracy of the data used by Darby *et al* (1992). In addition, the raw leukaemia registration data used in the study were retrieved from archives by Professor Darby and distributed to members. A number of members examined these data and the consensus was that, while there certainly existed a notable increase in reported infant leukaemia incidence in Denmark in the period 1961–1963, there were no increases in this period in the other four Nordic countries. It was therefore difficult to ascribe the Danish peak to atmospheric fallout from nuclear tests as this would have occurred also in other Nordic countries, indeed more so than in lower-rainfall Denmark. For the 1–4 year age group, the pattern of leukaemia incidence during the 1960s was consistent across the Nordic countries and compatible with that reported by Darby *et al* (1992).

38 Most of the Committee accepted the findings of the study of Darby *et al* (1992). However, two members still believed that the data were seriously flawed and that the estimates of risks were substantially too low. For them, the key issues remained the accuracy and completeness of registrations of specific types of leukaemia, and the accuracy of exposure estimates.

Great Britain

39 Two major studies have been carried out of childhood leukaemia in Great Britain following weapons testing fallout. Darby and Doll (1987) examined childhood leukaemia mortality and incidence after the peak of weapons testing and did not find evidence of a serious underestimation of risk. However, mortality from childhood leukaemia peaked in 1960 and then decreased due to improvements in treatment, and the quality of the British childhood leukaemia registration data for this period that were available at the time of this study is questionable, making the results difficult to interpret. Haynes and Bentham (1995) found that childhood leukaemia mortality and registration rates were generally greater in areas of Great Britain of lower rainfall than in areas of higher rainfall, ie in the opposite direction to what would be expected from an effect of fallout. However, during the period of highest fallout this pattern was reversed in the 0–4 year age group for mortality (but not for incidence), which was due to a fall in the mortality rate in the ‘wet’ area in combination with a rise in the mortality rate in the ‘dry’ area. This complex pattern of rates makes interpretation in terms of fallout problematical. The authors concluded that the results might be explained by survival and registration changes, or chance in the case of registrations, but they did not exclude the possibility that low doses of radiation from fallout

were responsible for an increased risk of leukaemia in young children in Great Britain. Haynes and Bentham (1995) did not venture beyond this tentative conclusion and did not attempt to quantify any effect of fallout.

40 In an attempt to improve the information available on childhood leukaemia incidence in Great Britain after the peak of atmospheric weapons testing fallout, the Committee requested the CCRG to supply childhood leukaemia registration data for the relevant period, to conduct its own analysis. The British childhood leukaemia registration data do not display unusual temporal patterns during the 1960s for either infant leukaemia or leukaemia in the 1–4 year age group. This does not suggest that fallout had a major impact upon the risk of childhood leukaemia in Great Britain.

41 In addition, the Committee considered a paper from one of its members, which compared leukaemia incidence rates for young children under five years of age obtained from the raw data made available for the Nordic countries and Great Britain with published leukaemia registration rates for this age group for Connecticut, Saskatchewan and New Zealand. These countries, states or provinces are those with reliable childhood leukaemia registration data covering the period of peak weapons testing fallout. The analysis demonstrates a consistency across the rates derived from the eight registries (including New Zealand in the Southern Hemisphere with much lower fallout) and there was no evidence of the notable increase in childhood leukaemia in the mid and late 1960s that would be predicted if the risk of exposure to fallout radionuclides had been greatly underestimated.

Summary

42 Overall, the studies of childhood leukaemia and fallout from atmospheric nuclear weapons testing suggest an increased risk due to the exposure, but provide no consistent or sufficiently persuasive evidence that this risk has been seriously underestimated by standard radiation risk models. The isolated peak in the Danish infant leukaemia rate during the early 1960s remains to be explained, but most of the Committee judged that it was unlikely to be due to fallout.

Conclusion

43 There is disagreement within the Committee about the results of the Chernobyl studies carried out to date. In the judgement of a large majority of Committee members, it is likely that the fallout from Chernobyl resulted in an increased risk of infant and childhood leukaemia incidence in the exposed populations. A substantial fraction of members thinks that this increase is around the level anticipated from current risk models. However, a substantial fraction feels that the level of this increased risk may have been underestimated by these models. Of this group, two members further believe that the evidence for infant leukaemia strongly suggests that the current risk estimates are appreciably in error. The remainder of the Committee believes that there exists relatively little evidence that lends support to this view. However, there is a consensus within the Committee that leukaemia incidence in infants post-Chernobyl merits further study.

44 On the atmospheric nuclear weapons testing fallout studies, a majority of the members of the Committee considered that there is insufficient evidence from these to suggest current risk estimates are too low. However, two members believed there was evidence from existing studies for an underestimation of risks of childhood leukaemia from weapons testing fallout. One member believed that current risk estimates were perhaps on the high side and that an association between exposure to low doses of radiation from weapons fallout and childhood leukaemia had not yet been proven.

4.5 Cancer Rates in Areas near Nuclear sites and in Coastal and Estuarine Areas

4.5.1 Cancer Rates in Areas near Nuclear Sites

Sellafield and Dounreay

45 All Committee members accepted the findings of many studies showing significant excesses of childhood leukaemia around Sellafield (in particular, an approximately 10-fold excess in the village of Seascale) in Cumbria, England, and Dounreay in Caithness, Scotland (Black Advisory Group, 1984; COMARE, 1988, 1996). These excesses were not generally reflected in other childhood or adult cancers (Black *et al*, 1992; Draper *et al*, 1993; COMARE, 1996). The question remained whether the increased rates of childhood leukaemia were caused by radiation exposure (eg from ingestion of radioactive material discharged to sea and/or inhalation of atmospheric emissions) or by other mechanisms. This matter has been examined in a number of COMARE reports, in particular the COMARE Fourth Report (1996), which concluded that, "the current best estimate of the radiation doses to the Seascale population is far too small to account for the observed numbers of cases of leukaemia and non-Hodgkin's lymphoma that have occurred in the young people of the village during the period of time studied".

46 Approximately half the Committee were of the view that the observed excesses were not linked to radiation. These members pointed to excesses of childhood leukaemia in areas remote from nuclear sites, and to nuclear sites where there are apparently no excesses (Laurier and Bard, 1999; Laurier *et al*, 2002). They believed that the population mixing hypothesis was a possible explanation for the excesses at Sellafield and Dounreay, and those elsewhere away from nuclear sites. This hypothesis posits that childhood leukaemia is a rare response to a common but unidentified infection and that the risk increases with high levels of mixing of urban and rural populations, the latter containing more individuals susceptible to the infection (Kinlen, 1988, 1995, 2000; Kinlen *et al*, 1993; Dickinson and Parker, 1999; Doll, 1999). The population mixing hypothesis has been tested in many studies, both at nuclear sites – eg Dounreay (Kinlen *et al*, 1993), Burghfield (Kinlen *et al*, 1991), and La Hague (Boutou *et al*, 2002) – and in other circumstances such as the wartime evacuation of children (Kinlen and John, 1994), areas around large-scale (non-nuclear) rural construction sites (Kinlen *et al*, 1995), and in isolated rural US counties (Wartenberg *et al*, 2004). The Committee did not make its own examination of the population mixing hypothesis, although it noted that COMARE (2002) had judged that, "The currently available evidence indicates that population mixing is responsible for a substantial part of the excess of LNHL (leukaemia and non-Hodgkin's lymphoma) among young people in Seascale. There is strong circumstantial evidence for the involvement of infectious agents in the population mixing effect, although the biological mechanism is not clear."

47 Other members of the Committee were of the view that the excesses may well be linked to radionuclides from nuclear facilities. They also considered that radiation may not be the sole causative factor of the excess leukaemias at Sellafield and Dounreay, but it could play a role in their aetiology.

48 Two members believed that there was a high probability that the childhood leukaemia excesses were linked to radiation from radioactive particulate material resulting from discharges to sea. They drew attention to the evidence of sea-to-land transfer of radionuclides, and to their own epidemiological studies of cancer incidence and mortality increases close to the coast and estuaries in various areas (see below and Annex 4C). The risks would be highest near sites where nuclear fuel was reprocessed rather than nuclear reactor sites because of the considerably higher radionuclide discharges from reprocessing. They pointed out that Pobel and Viel (1997), in a case–control study of

childhood leukaemia conducted around the La Hague reprocessing plant in Normandy, France, found statistical associations with the use of local beaches by pregnant women and children and with the consumption of local seafood by children. Urquhart *et al* (1991) found an association with children's use of local beaches in a similar study around Dounreay. However, these associations were based on self-reported habit information, and Gardner *et al* (1990) did not find such associations near Sellafield with higher marine discharges; these authors warned against potentially low quality data obtained in this way.

49 These two members also noted that the study of O'Donnell *et al* (1997) had found a significant decrease of plutonium concentration in teeth extracted for orthodontic purposes from young people living in Great Britain and Ireland with increasing distance of residence from Sellafield, which they believed was evidence of widespread contamination of people by plutonium from Sellafield. Another member pointed out that this result was heavily influenced by the data for teeth collected close to Sellafield and that this trend should not be over-interpreted. Other bioassay information did not support a notable presence in people of radioactive material discharged to sea, although autopsy investigations had found plutonium with an isotopic signature indicating an origin in the very early atmospheric releases from Sellafield in the lungs of long-standing residents of the area close to the site (Stather *et al*, 1988; Popplewell *et al*, 1989). A sensitive study of plutonium in the urine of children affected by leukaemia living near Dounreay and in Glasgow, and of healthy children and adults in these areas, did not detect any deviation in plutonium concentrations from those expected from background nuclear weapons testing fallout (Watson and Sumner, 1996).

Other Nuclear Sites

50 Studies have indicated increased rates of childhood leukaemia around certain other nuclear facilities: the La Hague reprocessing plant in Normandy, France (Guizard *et al*, 2001), the Krümmel nuclear power station in northern Germany (Grosche *et al*, 1999), and the Burghfield weapons facility in Berkshire, England (COMARE, 1989; Bithell *et al*, 1994). However, radiological assessments have been unable to attribute these excesses to radiation exposure, and increased levels of childhood leukaemia are not a general feature of areas in the vicinity of nuclear sites (Bithell *et al*, 1994; Sharp *et al*, 1996; Laurier and Bard, 1999; Laurier *et al*, 2002). As mentioned in paragraph 46 above, some of these excesses have been attributed to population mixing. A further complication was the finding of Cook-Mozaffari *et al* (1989) that the pattern of cancer mortality around potential nuclear sites in England and Wales (nuclear sites that were planned but not built, or were not operational) was 'strikingly similar' to the pattern around existing sites, suggesting the importance of factors other than radiation associated with the siting of nuclear facilities.

4.5.2 Cancer Rates in Coastal and Estuarine Areas in Great Britain

51 Two members requested the Committee to consider whether there were increased rates of cancer near the Bradwell power station. This request was based on their sea-to-land-transfer hypothesis that inter-tidal sediment may be contaminated with radionuclides from the power station under particular tidal conditions (ie not high energy tides) and that these sediments may be exposed when tides recede and may be blown inland to adjacent wards. The two members themselves had carried out, for Green Audit, a preliminary analysis of mortality data in the area for the period 1995–1999. The Committee was aware that there were conflicting reports from studies by Green Audit (Busby *et al*, 2001a, 2001b) and the Small Area Health Statistics Unit (SAHSU, 2001, 2002). COMARE evaluated these studies and in March 2003 it published a statement that, "there is no evidence of excess risk of cancer mortality in the vicinity of Bradwell power station in Essex" (COMARE, 2003b). (See also Annex 4C.)

52 Rather than revisiting the same data, the Committee proposed to undertake a wider study that was extended in time periods (1985–1999) and included cancer incidence as well as cancer mortality. The study was to be designed as a test of the sea-to-land-transfer hypothesis of the two members, in the context of Bradwell nuclear power station and the River Blackwater and River Crouch. Such a study required prior identification of precise named wards which fell into 'more-exposed' or 'less-exposed' categories, which were based on objective criteria, and which were agreed by all members of the Committee. Despite several meetings of the epidemiology sub-committee and many exchanges of email communications, agreement on the precise wards had not been reached by the epidemiology sub-committee meeting on 6 April 2004 when the Committee's final Report was nearing completion. At this meeting, it was agreed by the sub-committee that the ward list had to be completed sufficiently early to enable data to be compiled by the Office for National Statistics by 30 April 2004. The sub-committee also agreed that, if this did not occur, the study would have to be terminated, since there would then be insufficient time for the Committee to check, examine and properly analyse the cancer data before the results were included in its Report. Unfortunately, agreement on the precise wards was not reached in time.

53 The situation was further complicated by the late revelation that the two Committee members who had proposed the study had obtained access to some of the requested cancer incidence data at ward level, prior to the time they proposed changes to the ward list. Accordingly, the study was terminated through lack of time to resolve these issues. There was disappointment amongst Committee members that this initiative had failed, as it had represented an attempt to show that opposing groups could work together to achieve an agreed protocol and joint analyses of epidemiological data.

54 Some epidemiological studies (Alexander *et al*, 1990; Busby *et al*, 1998, 2000, 2001b) in coastal areas of the UK and near some estuaries close to nuclear sites appear to show increased incidences of cancers, including childhood leukaemias. However, most of these studies are not published in scientific journals and have not been peer reviewed. Two members of the Committee suggested that the higher incidences were linked to inhalation of radionuclides originating from effluent discharges to sea from nuclear sites especially Sellafield. Such discharged radionuclides remained on mud banks, especially under the Irish Sea. These mud deposits can be partially resuspended and washed ashore (Assinder *et al*, 1994), or be blown inland at low tide when mud banks are uncovered and dried out, or be blown ashore via sea spray (Eakins and Lally, 1984). The two members hypothesised that these exposures could be sufficient to cause detectably increased incidences of cancer.

55 Some members of the Committee strongly criticised the methodology and data used by Green Audit, members of which had produced many of the unpublished reports, and did not accept the validity of the findings of these studies. The methodology of the Green Audit studies was highly suspect and the results unreliable. These studies have also been heavily criticised by COMARE (2001, 2003a, 2004). A Committee member prepared detailed critical reviews of several Green Audit studies and found serious shortcomings in the reports, but the authors of the Green Audit studies did not, in general, accept these critiques. However, Green Audit did accept that the cancer mortality data used in early studies of the Bradwell area were in error and these were corrected. Further, serious discrepancies were found in the Welsh childhood leukaemia registration data used by Green Audit in a study that purported to show a pronounced excess risk of leukaemia in young children living in coastal communities in Wales. COMARE also concluded that these Welsh data (originally supplied to Green Audit by the former Welsh Cancer Registry) were clearly in error (COMARE, 2001). A second dataset with the original data discrepancies removed did not show a significantly raised risk in the group of Welsh coastal communities. The two Committee members who relied upon the Green Audit studies agreed that the first Welsh childhood leukaemia dataset should be set aside for

the purposes of CERRIE, although they did not accept that these data were necessarily in error. However, contemporaneous reports did not confirm the high rates of childhood leukaemia in Wales implied by the original registration data, and these data remain an isolated anomaly. On the basis of the second (agreed) Welsh dataset, there is little evidence for the initial claim of Green Audit of a raised risk of childhood leukaemia near the coast of Wales.

56 A study by Alexander *et al* (1990) found a marginally significant positive association between leukaemia at all ages and residence near estuaries, and a marginally significant negative association with residence near the coast. A follow-up study by Lloyd *et al* (2002) did not confirm the significant association with residence near estuaries, but did find a marginally significant positive association with residence near the coast. Consequently, there is no overall consistency between the results of the two studies. However, there are unavoidable differences between the two studies that make interpretation difficult. The Committee received a letter from Professor Alexander, which stated, "The totality of the information now available does not, therefore, support the hypothesis that living in an electoral ward adjacent to an estuary increases the risk of leukaemia. In my view, it is reasonable to extend this to say that the two papers together provide no support for the hypothesis that residence close to an estuary is linked to increased risk of leukaemia." A number of Committee members agreed with the conclusion of Professor Alexander.

57 The Committee understands from Professor Eve Roman at Leeds University that a PhD student is now working on a database of all childhood cancer cases diagnosed in the period 1992 to 1998. The Committee has contacted Professor Roman on the possibility of extending this work to examine the hypothesis about possible increases in estuarine areas.

4.5.3 Conclusion

58 There is a spectrum of views within the Committee on the reported excesses of childhood leukaemia near certain nuclear sites and cancer in coastal and estuarine areas of the UK. There is no dispute that raised rates of childhood leukaemia have occurred in the vicinity of specific installations, but the majority of members did not accept that the evidence showed that the risk of cancer in general was increased near nuclear sites, near estuaries or along the coast. About half the Committee members consider that the observed UK excesses were not linked to radiation, and are inclined to the view that population mixing may well provide most of the reason for the clear increased incidence of childhood leukaemia at a few nuclear sites, and elsewhere. The other half of the Committee is not convinced that radiation does not have a part to play in the excesses. Two members believe there are higher cancer rates around many nuclear sites near muddy estuaries or muddy inlets of low tidal energy and that these are linked to inhalation of sea-derived radioactive particulate material.

4.6 Nuclear Industry Workers and Their Children

59 The Committee is aware of the many studies of workers in the nuclear industry who have been exposed to radiation occupationally (eg Cardis *et al*, 1995; Muirhead *et al*, 1999). The largest of these studies have considered external radiation only; but recently the initial results of investigations of internal exposures have become available. Omar *et al* (1999) studied Sellafield plutonium workers using individual organ-specific doses assessed from urine analysis. They found that plutonium workers were at no greater risk of cancer than other radiation workers, including cancers affecting those tissues where plutonium accumulates. Of special interest are the studies of workers at the Mayak installation in Russia where workers were highly exposed to plutonium in the production of the first Soviet nuclear weapons. The results of these studies (Gilbert *et al*, 2000; Koshurnikova *et al*, 2000; Kreisheimer *et al*, 2003) are indicating clear excesses of cancers

of the lung, liver and bone as a consequence of heavy exposure to plutonium. At present, assessed organ doses are inadequate to derive reliable risk estimates for a broad range of tissues, but the Committee strongly supports the continued study of this important workforce. Of interest is the lack of an increased risk of leukaemia among the Mayak workers that is associated with plutonium exposure (Shilnikova *et al*, 2003) despite the markedly increased risk associated with external irradiation and the strong association between bone cancer and exposure to plutonium (Koshurnikova *et al*, 2000). This suggests that plutonium does not pose a high risk of leukaemia in adults.

60 Some members thought that the association between prostate cancer and tritium and certain fission products found in a study (Rooney *et al*, 1993) of UK Atomic Energy Authority workers indicated an underestimation of the risk of exposure to these radionuclides. The Committee noted that this association had not been confirmed by a study using more recent data (Atkinson *et al*, 2002).

61 The Committee did not have time to consider in detail studies of the effects of exposure to depleted uranium. The Committee noted that a Royal Society Working Group (2001, 2002) had recently examined this subject, drawn conclusions on the basis of the available evidence, and made appropriate recommendations for further research.

62 The finding of a correlation between the dose of external radiation received by Sellafield workers before the conception of their children and the incidence of leukaemia in these children by Gardner *et al* (1990) initially suggested that the irradiation of testes by internal emitters might have a role to play. However, subsequent studies of Sellafield workers, while confirming the external dose association, have not found a similar association with exposure to internal radioactive material (HSE, 1993, 1994; Hodgson *et al*, 1994; Dickinson and Parker, 2002). Moreover, the external dose association has not been confirmed by studies using data independent of those that generated the pre-conceptional irradiation hypothesis, and it cannot explain the excess cases of childhood leukaemia around Dounreay and La Hague because the great majority of affected children in these areas have fathers who were not exposed before conception (COMARE, 2002). COMARE, in its Seventh Report (2002), has concluded, “We find no convincing evidence to suggest that ionising radiation alone at the doses to which male radiation workers have been exposed results in an increased incidence of childhood cancer.”

4.7 Non-cancer Effects

63 The only low dose non-cancer effects incorporated in current ICRP risk coefficients are hereditary genetic anomalies. However, the ICRP radiological protection regime does take account of recognised deterministic effects (such as cataracts of the lens of the eye), which are characterised by threshold doses. Further, this regime also takes into account effects (such as malformations and severe mental retardation) that can be induced by irradiation *in utero*. Most of the doses required for these non-cancer effects are relatively high (often greater than 1 Gy), although a recent paper by Hall *et al* (2004) indicated a dose–response for adverse effects on cognitive function in adulthood following external irradiation in infancy at doses down to 100 mSv. The Committee accepts that these non-cancer effects could be induced by radiation from internal emitters provided the relevant sensitive cells are sufficiently exposed.

64 The Committee considered epidemiological evidence on the dose–response for certain somatic non-cancer effects such as cardiovascular disease, stroke, and respiratory and digestive diseases. This evidence largely derives from studies of exposure to external radiation, such as the Japanese A-bomb survivors (Preston *et al*, 2003), rather than internal radiation. Based on the A-bomb survivor data, the Committee estimated that the lifetime absolute risk for non-cancer mortality following acute exposure to radiation as children may be around 10% at 1 Sv, ie roughly half the corresponding value for solid

cancer mortality. For people exposed at age 50 years, the lifetime risks may be similar for non-cancer and for solid cancer mortality (ie around 3–4% at 1 Sv) (Preston *et al*, 2003). Whether a risk of these non-cancer effects exists at low doses will depend on the biological mechanisms of their induction by radiation, which have yet to be determined.

65 Two Committee members consider that epidemiological evidence exists for a materially increased risk of non-cancer effects after exposure *in utero* to radioactive fallout, which would not be predicted by current risk models. They point, in particular, to the studies of Sternglass (1969) on infant mortality and Whyte (1992) on mortality during the first day after birth, in support of this view. Other members noted that Sternglass reported a change in the rate of decrease of infant mortality, and that this change was different in countries that experienced broadly the same level of exposure to weapons testing fallout. Further, a variation in the rate of decrease in infant mortality was similarly observed in Australia, which experienced much lower levels of fallout. Also, the timing of the changes in the rate of first-day neonatal mortality reported by Whyte (1992) does not coincide with fallout exposure. The two Committee members also referred to other studies of the non-cancer effects of fallout from weapons testing and Chernobyl, which they believed supported the existence of such effects following low level internal exposure. Insufficient time was available to the Committee to examine fully these studies, but when one study conducted in the vicinity of the Mayak nuclear facility (Petrushkina *et al*, 2000) was considered in detail, it was found to provide only weak support to this view. Therefore, the rest of the Committee does not accept that there is sufficient evidence to support this interpretation of the infant mortality data.

66 The Committee received from a member of the public a copy of his self-published study on a possible association between male perinatal mortality in Cardiff and previous discharges of tritium to atmosphere. The Committee was informed that an independent review of this study, commissioned by the Bro Taf Health Authority, had made a number of recommendations for further research. Accordingly, the Committee wrote to the Bro Taf Health Authority to enquire whether the Authority was proposing to implement the recommendations and to request a copy of any report on research findings. The reply, from the National Public Health Service (NPHS) for Wales, was that the NPHS was pursuing all of the recommendations and it indicated that the Committee would be kept informed of all relevant work being undertaken by the NPHS. No further communications had been received up to the time of the Committee's last meeting.

4.8 Conclusions on Epidemiological Evidence

67 All members of the Committee believe that the epidemiological evidence is compelling for moderate and high levels of exposure to internally incorporated radionuclides producing a raised risk of adverse health effects in those exposed. All members, but one, of the Committee believe that the low level intake of radionuclides leads to some increased risk of adverse health effects as a result of the internal irradiation of organs and tissues. Some members think that the epidemiological evidence, taken as a whole, does not suggest that the predictions of current risk models are materially in error. Other members consider that few certain conclusions on risks may be derived from the epidemiological evidence. They consider current risk models may well underestimate risks from intakes of certain radionuclides, but by relatively modest factors. On the other hand, two members think that current models underestimate risks from intakes of radionuclides by very large factors. Conversely, one member thinks that any observed increases in risks at low doses are most likely to have causes other than radiation, ie current models overestimate risks at low doses. Consequently, there is little consensus amongst members on the epidemiological evidence as a whole.

68 The disagreements stem from differences of view about the appropriateness of the data and methodologies used in epidemiological studies and about interpretations of their

findings. It is not anticipated that these can be resolved by further discussion. A core methodological concern is that the inherent limitations of epidemiological studies at low levels of exposure make it difficult to reliably quantify health risks. Most of the Committee consider that the nature of the epidemiological evidence, taken as a whole, inevitably leads to uncertainties in current internal radiation risk models, although there are different views on the magnitude of these uncertainties. There is a consensus within the Committee that epidemiological evidence is strengthened when supplemented by laboratory and theoretical information on underlying mechanisms to guide estimates of risk at low doses.

69 The Committee has some general and some specific recommendations about future epidemiological studies (see below). It is hoped that adherence to these recommendations may resolve disagreements in some areas. However, it seems likely that disagreements in other areas will remain for some years to come.

4.9 Recommendations on Future Epidemiological Studies

70 The Committee was unable to complete its proposed study of cancer incidence and mortality near the Bradwell facility due to lack of time to agree study parameters and obtain the data for analysis. In view of this, it recommends that further epidemiological studies be considered in an attempt to resolve the question of whether cancer rates are generally higher in coastal and estuarine areas and in the vicinities of nuclear sites. Members are aware that a study by COMARE of the geographical distribution of childhood cancer cases in Britain, particularly near nuclear sites, is currently nearing completion. When this study is completed the results should be reviewed to determine whether they justify a broader study of adult cancers around nuclear sites and contaminated estuaries.

71 The Committee has become aware of a few instances where errors have been made in epidemiological analyses carried out by governmental and non-governmental organisations, and where these errors have not been discovered until after the findings have been made public. The Committee has also become aware of one instance in which the data provided to epidemiologists by a government-funded organisation were subsequently found to be incorrect, or at least presented in a confusing way. The Committee supports the COMARE recommendation that organisations and research groups should establish scientific protocols and internal controls to prevent such errors before distributing data or conducting epidemiological analyses and making public their results. In addition, the Committee recommends that such results should be published in recognised peer-reviewed scientific publications. However, the Committee recognises that the peer-review process may tend to reject evidence that does not conform to existing paradigms. Where epidemiological results are self-published, authors have a scientific and public responsibility to ensure that their analyses are carefully checked and closely examined prior to publication by other scientists willing to review their work.

72 A difficulty for those outside the epidemiological field who seek to judge the quality of epidemiological results is that some of the organisations involved do not trust each other. This has led to unproductive and emotive arguments in print, often in newspapers rather than scientific journals. The Committee recommends that there should be better communication between the various organisations that conduct epidemiological analyses. It stresses the importance of using rigorous scientific methods, including the establishment of prior hypotheses, proper statistical analysis, objective interpretation and peer review of proposed articles. The Committee considers that there is scope for more joint analyses by governmental organisations and other groups. However, it also notes that recent administrative provisions on ethical and data protection are making it difficult in practice to carry out epidemiological research. These difficulties were emphasised by a number of participants at the CERRIE Workshop (see Appendix B).

73 The Committee recommends that groups of individuals exposed to radiation from internally deposited radionuclides should continue to be the subject of epidemiological studies. A number of such groups have already been investigated in some depth, including patients and workers exposed to radioisotopes of radium, patients exposed to thorium in the contrast medium Thorotrast, and workers and members of the public exposed to radon and its decay products. The Committee encourages the continued study of these groups where profitable, and is aware that substantial effort is being expended in the study of groups exposed to radon. Since exposure to radon is the most extensive exposure to radiation, this continued programme of epidemiological work is welcomed. In addition, the Committee recommends that consideration be given to epidemiological studies of potential heritable effects following exposure to internal emitters – for example, among the offspring of Mayak workers and of Techa River residents in Russia.

74 Nuclear industry workers are exposed to a range of radionuclides and the Committee recommends that studies of workers exposed to internal emitters continues. There is scope for further evidence to be obtained from internally exposed workers in the UK, the rest of Europe (especially France) and North America, and such epidemiological studies should be supported appropriately. In recent years, important data from workers exposed in the FSU have become available. These include the Chernobyl clean-up workers and, in particular, the workers at the Mayak nuclear facility in the Southern Urals. The latter group experienced particularly high levels of exposure to plutonium, and careful assessments of the organ-specific doses received by these workers and of their health status could lead to reliable risk coefficients for plutonium. The Committee recommends that the Mayak workforce should continue to be carefully studied. It may be the case that other groups of workers become available for study in future (for example, nuclear workers in China) and the scientific community should remain alert to these possibilities.

75 It should be noted that patients and medical workers are increasingly exposed to internal emitters as a result of diagnostic investigations and therapeutic treatments. It may be that epidemiological study of these groups would be of value. The Committee recommends that this possibility should be investigated.

76 A number of groups of members of the public have been exposed to radionuclides of man-made origin. In particular, groups exposed in the FSU are of special interest because large numbers of people experienced a range of exposures. Those exposed to Chernobyl fallout should continue to be the subject of study, particularly those heavily exposed as children. Other specific examples are the residents of the area that received fallout from the Semipalatinsk nuclear weapons test site in Kazakhstan and the inhabitants of communities neighbouring the Techa River. The Techa River received large quantities of highly radioactive waste from the Mayak facility in the late 1940s and early 1950s, which resulted in high exposures to local residents. The Committee supports the continuing effort to study these groups.

77 The Committee considers that a valuable complement to epidemiological studies of those exposed to internal emitters is the measurement of the presence (and levels) of radionuclides in study subjects through appropriate bioassay techniques. This is becoming increasingly common in studies of workers, a trend that is to be encouraged, but has not often been carried out in studies of those environmentally exposed. Such bioassay measurements would provide an important aid to the interpretation of epidemiological studies, and many of these methods (such as the measurement of radionuclides in urine or in teeth removed for orthodontic purposes) are not invasive and could be carried out relatively easily. The possibility of such bioassay measurements being made on appropriate samples from members of the public resident in various parts of the country, to determine general levels of radionuclides around, and distant from, nuclear sites should also be considered. The Committee recommends that greater use be made of presently available bioassay techniques.

78 A related and complementary issue is the possibility of performing biodosimetry measurements on study subjects. Certain measures of biological damage (such as chromosomal aberration rates in peripheral blood lymphocytes) have been developed which can be related to the dose received by the relevant cells. However, this is not straightforward for internal emitters such as plutonium since the dose may not be delivered to the cells that are the basis of the assay. Further, such techniques usually involve the sampling of blood, which could present ethical difficulties under certain circumstances. Nonetheless, biodosimetry has proved to be of value in specific instances, and the Committee recommends that the suitability of techniques for measuring biological damage related to clinical effects be monitored to assess whether they can be applied to epidemiological studies of internal emitters.

ANNEX 4A
Post-Chernobyl Epidemiology

(1) This annex gives further details of studies of infant leukaemia (ie cases diagnosed in the first year of life) following the Chernobyl accident.

Mainland Europe and USA

(2) In the study conducted in Greece, Petridou *et al* (1996) examined rates of infant leukaemia among children born in the 18-month period between 01/07/1986 and 31/12/1987, who received radiation exposure *in utero* as a consequence of the Chernobyl nuclear power plant accident in April 1986. Incidence rates in this 'exposed' cohort were compared with rates among those in an 'unexposed' cohort of children born either during 1980–1985 or during 1988–1990. Studies conducted subsequently in West Germany (Steiner *et al*, 1998), Belarus (Ivanov *et al*, 1998) and parts of the USA (Mangano, 1997) have analysed data in a similar manner. The findings from these studies are summarised in Table 4A.1.

Table 4A.1 Infant leukaemia following the Chernobyl accident by birth cohort

	Cases in 'exposed' birth cohort	**Ratio of incidence rates in 'exposed' and 'unexposed' birth cohorts (95% confidence interval or two-sided p-value)**
Greece	12	2.6 (1.4, 5.1)
Areas with mean activity of ^{137}Cs in surface soil:		
<0.1 Bq g^{-1}	*1*	*~1.2*
0.1–1 Bq g^{-1}	*7*	*~2.6 (p=0.02)*
>1 Bq g^{-1}	*4*	*~4.2 (p=0.004)*
West Germany	35	1.48 (1.02, 2.15)
Areas with mean ground deposition of ^{137}Cs:		
< 6 kBq m^{-2}	*29*	*1.84 (1.21, 2.78)*
6–10 kBq m^{-2}	*1*	*0.25 (0.03, 1.89)*
>10 kBq m^{-2}	*5*	*1.29 (0.49, 3.40)*
Belarus	17	1.26 (0.76, 2.10)
Mogeljev/Gomel	*6*	*1.51 (0.63, 3.61)*
USA (part)	62 [a]	1.30 (p<0.09)
Great Britain	41	1.22 (0.86, 1.69)
Areas defined by level of exposure:		
Low	*16*	*1.02 (0.58, 1.68)*
Intermediate	*24*	*1.40 (0.88, 2.15)*
High	*1*	*1.19 (0.06, 7.4)*

a Includes cases born at any time in 1986 or 1987.

(3) In contrast to the above findings for infant leukaemia, the birth cohort studies conducted in Greece, West Germany and Belarus did not show raised risks of leukaemia among young children at ages 1–3 or 1–4 years; see Table 4A.2.

Table 4A.2 Leukaemia incidence in young children (1–3 or 1–4 years of age) following the Chernobyl accident, by birth cohort

	Cases in 'exposed' birth cohort (births during 01/07/86–31/12/87)	**Ratio of incidence rates in 'exposed' and 'unexposed' birth cohorts (95% confidence interval)**
Greece [a]	43	1.1 (0.8, 1.5)
West Germany [b]	290	0.98 (0.87, 1.11)
Belarus [a] (*Mogeljev and Gomel*)	53 *18*	1.06 (0.81, 1.39) *1.21 (0.73, 2.00)*

a Ages 1–3 years.

b Ages 1–4 years.

(4) Data are not yet available from an ongoing combined analysis of infant leukaemia data from 23 European countries following the Chernobyl accident, as part of the European Childhood Leukaemia/Lymphoma Incidence Study (ECLIS). However, Parkin *et al* (1996) gave findings from an analysis of infant leukaemia in relation to *in utero* dose arising from the accident, as shown in Table 4A.3. In particular, a test for trend in infant leukaemia risk with dose gave χ^2 = 0.26 on 1 degree of freedom (p = 0.61). Table 4A.3 also shows results for leukaemia at ages 0–14 years. In this instance, the χ^2 for trend was 0.85 on 1 degree of freedom (p=0.36).

Table 4A.3 Leukaemia incidence in infants and children (0–14 years of age) following the Chernobyl accident, by dose category, in ECLIS (Parkin *et al*, 1996)

Cumulative excess dose (mSv)	**Age (years)**			
	<1		**0–14**	
	Observed cases	**Ratio of observed to expected cases**	**Observed cases**	**Ratio of observed to expected cases**
0	775	1.00	15,004	1.000
0.01–0.05	513	1.01	3,870	1.002
0.06–0.12	43	0.80	2,172	1.009
0.13–0.29	6	0.79	2,022	0.992
0.30+	13	1.79	2,752	0.995

Great Britain

(5) Prior to the establishment of CERRIE, data were not available in the above format by birth cohort for Great Britain. However, results had been published according to the period in which infant leukaemias were diagnosed. For Scotland, Gibson *et al* (1988) reported that six cases were observed during 1987, compared with 1.4 expected, and that this excess continued into the first half of 1988 when three cases were observed. The Scottish cases were also reported by Busby and Scott Cato (2000), who additionally cited data for Wales; in particular, four cases of infant leukaemia observed during 1988 and none during 1987. Data had not been reported in a systematic fashion for England. However, analyses of birth cohorts in England, Scotland and Wales have been conducted recently under the auspices of CERRIE, using incidence data collected by the Childhood Cancer Research Group (CCRG). These analyses have considered the birth periods studied by Petridou *et al*, and have also involved looking separately at a further exposed birth cohort consisting of those born during 01/01/88–31/12/90 and an unexposed cohort of those born during 01/01/91–31/12/97.

(6) Table 4A.1 shows results from analysis of the CCRG data, both for the whole of Great Britain and for a sub-division of the British data into three geographical regions, defined according to the level of exposure arising from the Chernobyl accident (see Table 4A.4 for definitions of these regions). Estimates of relative risks and excess rates for the British data in these tables were calculated by maximum likelihood, based on Poisson distributions for the numbers of infant leukaemia cases. Incidence rates by birth cohort and geographical region are displayed in Figure 4A.1. The risk of infant leukaemia amongst those born during 01/07/86–31/12/1987 is consistent with the risk among those born in either during 01/01/80–31/12/85 or 01/01/88–31/12/90, as well as with both higher and lower levels of risk. In particular, the relative risk in the former birth cohort relative to the latter two cohorts was estimated as 1.22 (95% CI 0.86, 1.69) for the whole of Great Britain. In absolute terms, this corresponds to an estimated additional 6.7 cases per million births, with a 95% confidence interval ranging from 4.5 fewer cases to 19.7 additional cases per million births. Further details are given in Table 4A.4, in which comparisons are made both across geographical regions within each birth cohort, and across birth cohorts within each geographical region. It is notable that there were very few cases in the region of highest exposure, namely, North Wales, Cumbria and Southwest Scotland.

(7) In addition to the birth periods considered by Petridou *et al*, the British data have been analysed for the following four birth cohorts: 01/05/81–30/04/86, 01/05/86–31/12/87, 01/01/88–31/12/90 and 01/01/91–31/12/97. Incidence rates by birth cohort and geographical region are displayed in Figure 4A.2. In this analysis, attention was directed at comparing infant leukaemia risks in the second and third of these cohorts (ie those born in 01/05/86–31/12/90) relative to the first and fourth birth cohorts. The associated relative risk was estimated as 1.07 (95% CI 0.86, 1.32) for the whole of Great Britain, which – in absolute terms – corresponds to an estimated additional 2.2 cases per million births, with a 95% confidence interval ranging from 4.8 fewer cases to 9.7 additional cases per million births. The corresponding relative risks split by geographical region were 1.14 (95% CI 0.82, 1.55) for the 'low' exposure region, 0.99 (0.73, 1.33) for the 'intermediate' exposure region and 1.40 (0.37, 4.64) for the 'high' exposure region. Further details, including observed numbers of cases and excess absolute rates, are given in Table 4A.5. Again all of the relative risks are consistent with values either side of 1.

(8) Whilst the British birth cohort study has produced results that are generally in the direction expected from Chernobyl contamination increasing the risk of infant leukaemia, the numbers of cases are so small that the findings cannot exclude the possibility of there being no increase in risk at all. Consequently, the British birth cohort study adds little information to the evidence concerning the effect of Chernobyl radionuclides upon the risk of infant leukaemia.

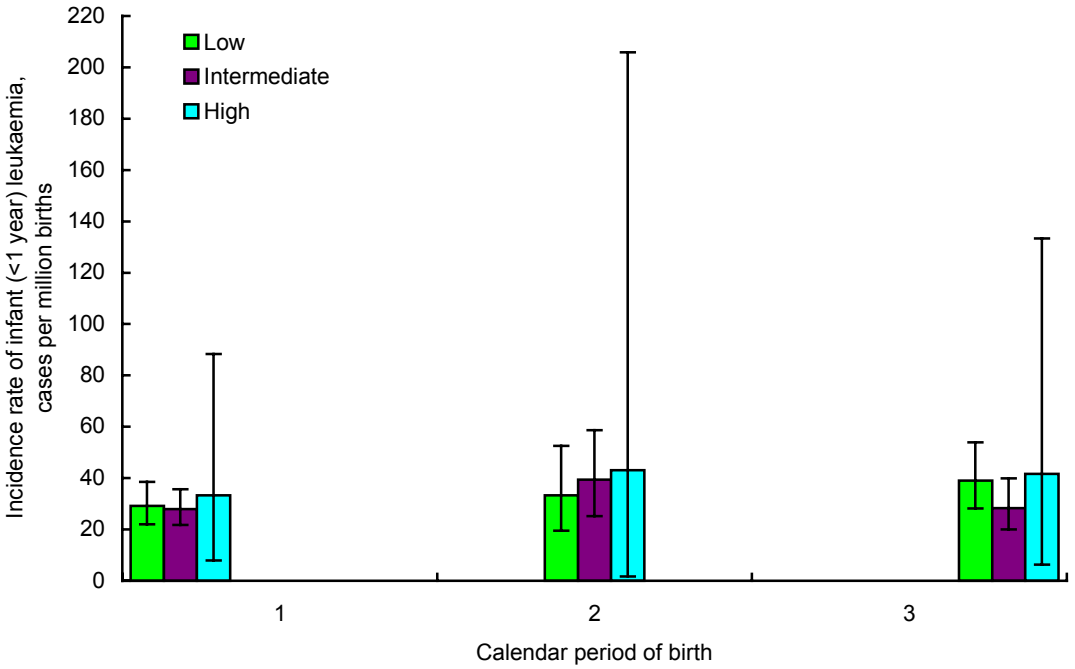

Figure 4A.1 Rate of incidence of infant (<1 year of age) leukaemia in Great Britain by three periods of birth and by three areas of birth, categorised by the level of Chernobyl contamination (see Table 4A.4). Error bars show 95% confidence intervals on rates

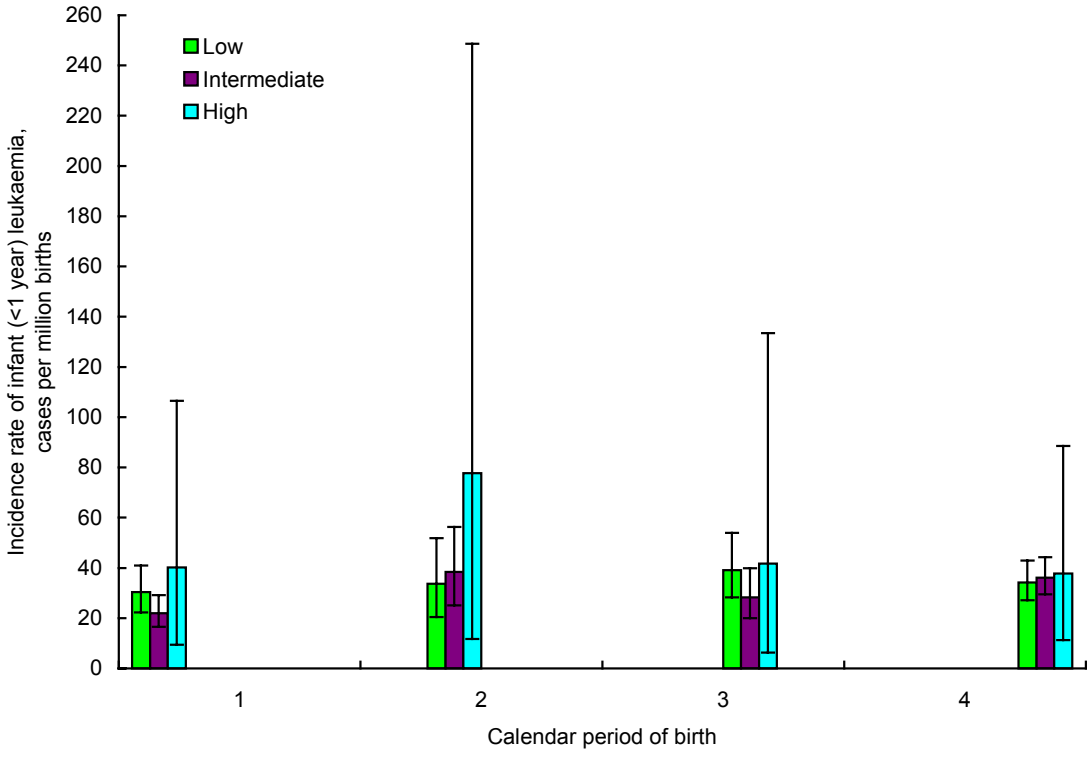

Figure 4A.2 Rate of incidence of infant (<1 year of age) leukaemia in Great Britain by four periods of birth and by three areas of birth, categorised by the level of Chernobyl contamination (see Table 4A.5). Error bars show 95% confidence intervals on rates

Table 4A.4 Infant leukaemia in Great Britain, by birth cohort (using the Petridou *et al* definition of periods of birth) and geographical region

Birth cohort		Geographical exposure category		
		Low	**Intermediate**	**High**
01/01/80–31/12/85	No. of cases	52	66	3
	RR1 (95% CI)	1.00	0.96 (0.67, 1.38)	1.14 (0.28, 3.10)
	RR2 (95% CI)	*1.00*	*1.00*	*1.00*
01/07/86–31/12/87	No. of cases	16	24	1
	RR1 (95% CI)	1.00	1.18 (0.63, 2.27)	1.30 (0.07, 6.36)
	RR2 (95% CI)	*1.14 (0.63, 1.95)*	*1.41 (0.87, 2.21)*	*1.30 (0.06, 10.1)*
01/01/88–31/12/90	No. of cases	39	35	2
	RR1 (95% CI)	1.00	0.72 (0.46, 1.14)	1.07 (0.17, 3.47)
	RR2 (95% CI)	*1.34 (0.88, 2.02)*	*1.01 (0.67, 1.52)*	*1.25 (0.16, 7.53)*
Comparison of risks for births during 01/07/86–31/12/87 with those for births during 01/01/80–31/12/85 and 01/01/88–31/12/90	Relative risk (95% CI)	1.02 (0.58, 1.68)	1.40 (0.88, 2.15)	1.19 (0.06, 7.4)
	Excess cases per million births (95% CI)	0.6 (–15.1, 20.7)	11.4 (–3.6, 30)	7.0 (<0, 156)

RR1 Relative risk for each geographical exposure category, relative to the category 'low', within each birth cohort.

RR2 Relative risk for each birth cohort, relative to those born during 01/01/80–31/12/85, within each geographical exposure category.

95% confidence limits calculated using the profile likelihood.

High exposure region: Cumbria, Clwyd, Gwynedd, Dumfries and Galloway.

Intermediate exposure region: Greater Manchester, Merseyside, South Yorkshire, Tyne & Wear, West Midlands, West Yorkshire, Cheshire, Cleveland, Derbyshire, Durham, Gloucestershire, Hereford & Worcester, Humberside, Lancashire, Leicestershire, Lincolnshire, Northumberland, North Yorkshire, Nottinghamshire, Shropshire, Staffordshire, Warwickshire, Dyfed, Gwent, Mid Glamorgan, Powys, South Glamorgan, West Glamorgan, Borders, Central, Fife, Grampian, Highland, Lothian, Strathclyde, Tayside, Orkney, Shetland, Western Isles.

Low exposure region: Inner and Outer London, Avon, Bedfordshire, Berkshire, Buckinghamshire, Cambridgeshire, Cornwall, Devon, Dorset, East Sussex, Essex, Hampshire, Hertfordshire, Isle of Wight, Kent, Norfolk, Northamptonshire, Oxfordshire, Somerset, Suffolk, Surrey, West Sussex, Wiltshire.

Table 4A.5 Infant leukaemia in Great Britain, by birth cohort (using the CERRIE definition of periods of birth) and geographical region

Birth cohort		Geographical exposure category		
		Low	**Intermediate**	**High**
01/05/81–30/04/86	No. of cases	45	52	3
	RR1 (95% CI)	1.00	0.87 (0.59, 1.31)	1.32 (0.32, 3.62)
	RR2 (95% CI)	*1.00*	*1.00*	*1.00*
01/05/86–31/12/87	No. of cases	18	26	2
	RR1 (95% CI)	1.00	1.14 (0.63, 2.10)	2.31 (0.37, 7.99)
	RR2 (95% CI)	*1.11 (0.63, 1.89)*	*1.44 (0.89, 2.29)*	*1.93 (0.25, 11.6)*
01/01/88–31/12/90	No. of cases	39	35	2
	RR1 (95% CI)	1.00	0.72 (0.46, 1.14)	1.07 (0.17, 3.47)
	RR2 (95% CI)	*1.29 (0.83, 1.98)*	*1.07 (0.69, 1.63)*	*1.03 (0.14, 6.24)*
01/01/91–31/12/97	No. of cases	78	98	4
	RR1 (95% CI)	1.00	1.05 (0.79, 1.43)	1.10 (0.34, 2.65)
	RR2 (95% CI)	*1.12 (0.78, 1.64)*	*1.36 (0.98, 1.92)*	*0.93 (0.21, 4.75)*
Comparison of risks for births during 01/05/86–31/12/90 with those for births during 01/05/81–30/04/86 and 01/01/91–31/12/97	Relative risk (95% CI)	1.14 (0.82, 1.55)	0.99 (0.73, 1.33)	1.40 (0.37, 4.64)
	Excess cases per million births (95% CI)	4.6 (–6.2, 16.4)	–0.2 (–9.4, 9.7)	15.6 (–38.2, 91.2)

RR1 Relative risk for each geographical exposure category, relative to the category 'low', within each birth cohort.

RR2 Relative risk for each birth cohort, relative to those born during 01/05/81–30/04/86, within each geographical exposure category.

95% confidence limits calculated using the profile likelihood.

Exposure regions as in Table 4A.4.

Comparison of Findings

(9) Table 4A.6 shows the infant leukaemia excess relative risks (ERR), ERR coefficients (representing the trend in ERR per unit dose) and the possible external ERR coefficient discrepancy factors (ie the ratios of the estimated Chernobyl contamination ERR coefficients to the external ERR coefficient), for each of Great Britain, Greece, West Germany and Belarus. To derive excess relative risk coefficients (ERR Sv^{-1}) from the Chernobyl fallout studies, it is necessary to estimate the doses received from Chernobyl contamination. Approximate estimates of the country-average whole-body dose (excluding the thyroid dose) from Chernobyl fallout – namely, 2 mSv for Belarus, 0.2 mSv for Greece, 0.1 mSv for West Germany, and 0.02 mSv for Great Britain – have been used in deriving the ERR coefficients in Table 4A.6. The dose estimates for Greece and Great Britain correspond approximately to the values given in the EU report of Morrey *et al* (1988), while the German estimate also takes account of the calculations of Steiner *et al* (1998). The 1988 UNSCEAR report was the source of the dose estimate for Belarus. It must be recognised that there is uncertainty (possibly a factor of two to three – see UNSCEAR, 1988) associated with these dose estimates. Taking account of this additional source of uncertainty would serve to widen the confidence intervals associated with the Chernobyl ERR coefficients that are given in Table 4A.6.

(10) The exposed cohorts in Table 4A.6 are births during 01/07/86–31/12/87, while the unexposed reference cohorts are births during 01/01/80–31/12/85 or 01/01/88–31/12/90 in Great Britain, Greece and West Germany, and during 01/01/82–31/12/85 or 01/01/88–31/12/94 in Belarus. Also, based on findings from the Oxford Survey of Childhood Cancers (OSCC), an ERR coefficient of 50 Gy^{-1} has been taken for infant leukaemia after irradiation *in utero* by an external source of X-rays (Wakeford and Little, 2003), under the assumption that the ERR coefficient for infants <1 year of age is not greatly different from that for children 0–14 years of age. For the purposes of this comparison, the ERR coefficient from the OSCC is taken to be without error, although the uncertainty associated with this risk estimate should be borne in mind when considering the confidence intervals associated with the ratios of ERR coefficients presented below, which will increase in width.

Table 4A.6 Excess relative risks of infant leukaemia estimated in four birth cohort studies

Study	ERR (95% CI)	ERR coefficient (95% CI) Sv^{-1}	Ratio to external ERR coefficient (95% CI)
Great Britain	0.22 (–0.14, 0.69)	11,000 (–7,000, 34,500)	220 (–140, 690)
Greece	1.6 (0.4, 4.1)	8,000 (2,000, 20,500)	160 (40, 410)
West Germany	0.48 (0.02, 1.15)	4,800 (200, 11,500)	96 (4, 230)
Belarus	0.26 (–0.24, 1.10)	130 (–120, 550)	2.6 (–2.4, 11)

(11) From the studies conducted in the three countries with higher average Chernobyl fallout doses than in Great Britain, the upper 95% confidence limits place tighter constraints upon the factor that the excess relative risk of infant leukaemia may have been underestimated by the ERR coefficient derived from the Oxford Survey: in Greece this factor is ~400, in West Germany it is ~200, and in Belarus it is ~10. The low statistical power (and hence the wide confidence intervals) in all but the Belarus study is readily apparent in Table 4A.6. It should be noted that it is only the Greek study that produces an ERR coefficient that is discrepant with the external irradiation ERR coefficient by a comparatively large factor: the lower 95% confidence limit for the ratio of coefficients is 40. It should also be noted that the Greek ERR coefficient is statistically incompatible with that obtained for Belarus; it is the Greek results that appear to be out of line in producing an anomalously raised risk estimate. Any suggestion, therefore, that the risk of infant leukaemia arising from exposure to radionuclides in Chernobyl fallout has been materially underestimated is largely based upon the findings of just one study.

ANNEX 4B
Weapons Test Fallout Epidemiology

(1) This annex gives some further details of studies of childhood leukaemia in relation to fallout from atmospheric nuclear weapons tests. Figure 4B.1 shows the temporal distribution of effective doses in the Northern Hemisphere due to atmospheric nuclear weapons testing (UNSCEAR, 2000).

Nordic Countries

(2) Data from the Nordic countries have been studied as a means of looking for any association between trends in childhood leukaemia rates and fallout from atmospheric nuclear weapons tests because national registration systems in these countries provided good coverage of cancers dating back to the 1950s or early 1960s. Doses from weapons fallout tended to be higher in these countries than in those at more southerly latitudes, mainly due to higher rainfall.

(3) Figure 4B.2 shows the temporal patterns of leukaemia rates at ages 0–4 years in several countries, including the four largest Nordic countries. Data from Denmark indicate raised rates of childhood acute leukaemia around the time of peak fallout (Hakulinen *et al*, 1986). In particular, Hansen *et al* (1983) reported a three-fold increase in the incidence of acute leukaemia at ages 0–9 years during 1943–1977. However, this analysis excluded leukaemia registrations with type unspecified, which formed a substantial proportion of all leukaemia registrations up to 1970. As indicated in Figure 4B.2 and by de Nully Brown *et al* (1989), time trends in the incidence of childhood leukaemia of all types in Denmark were not so marked.

(4) Darby *et al* (1992) carried out a combined analysis of data from the Nordic countries on childhood leukaemia incidence in relation to temporal patterns of fallout from atmospheric nuclear weapons testing. Data were included from 1948 for Denmark, from 1958 for Finland, Norway and Iceland, and from 1961 for Sweden. Data were assumed to be complete up to the end of 1980 (Iceland), 1984 (Denmark) or 1987 (Sweden, Norway and Finland). Figure 4B.2 shows leukaemia rates by country at ages 0–4 years by calendar period of diagnosis. Analysis of these data by individual calendar year of birth indicates a raised rate of leukaemia at ages 0–4 years amongst those born in 1965 and 1966 in Denmark (see Figure 4B.3); however, no such peak is seen in the other Nordic countries for those born around the same time.

(5) Darby *et al* (1992) fitted a series of models to investigate the possible effects of irradiation from weapons fallout received after birth, *in utero* or to the father's testes. This was based on classifications – by calendar year – of the estimated dose equivalents to the fetus, 1-year old and adult testes. The five exposure categories used in the analysis were described as: Low-1, Medium-1, High, Medium-2 and Low-2, reflecting the rise in fallout doses in years leading up to the early 1960s and the subsequent fall in doses (see Table 4B.1). Table 4B.2 shows the relative risk of leukaemia at ages 0–14 years and 0–4 years, relative to the Low-1 exposure category. When compared with the two medium exposure categories combined, the relative risk for the high exposure category was 1.07 (95% CI 1.00, 1.14) at ages 0–14 years and 1.11 (95% CI 1.00, 1.24) at ages 0–4 years. These relative risks compare with a value of 1.03[1] predicted to result from a dose of 1 mSv by the BEIR V Committee leukaemia risk model (NRC, 1990).

[1] The associated 95% confidence interval for the relative risk of childhood leukaemia calculated from the BEIR V leukaemia model is (1.004, 1.26).

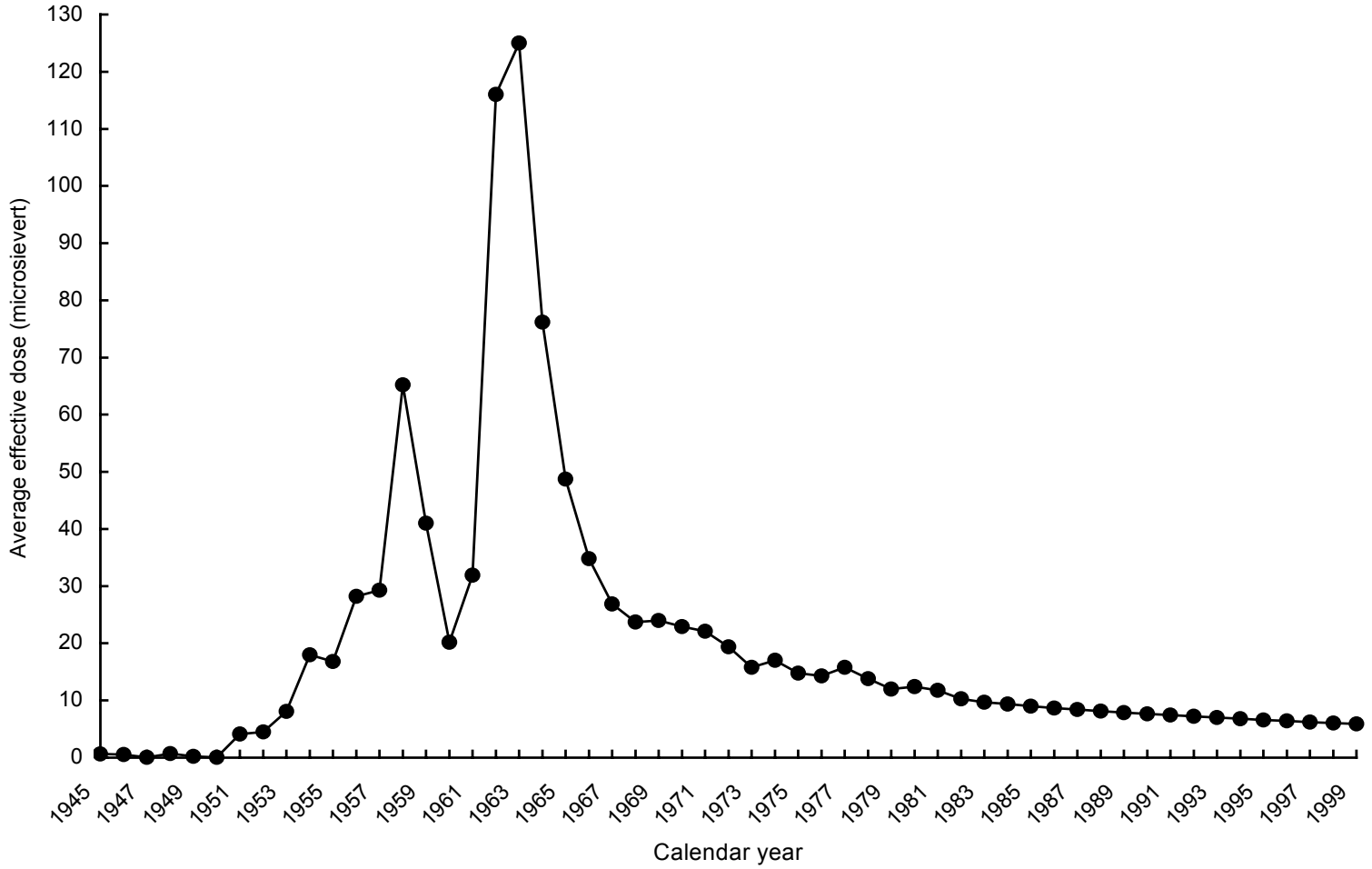

Figure 4B.1 Average annual effective dose in the Northern Hemisphere from radionuclides produced in atmospheric nuclear weapons testing (UNSCEAR, 2000)

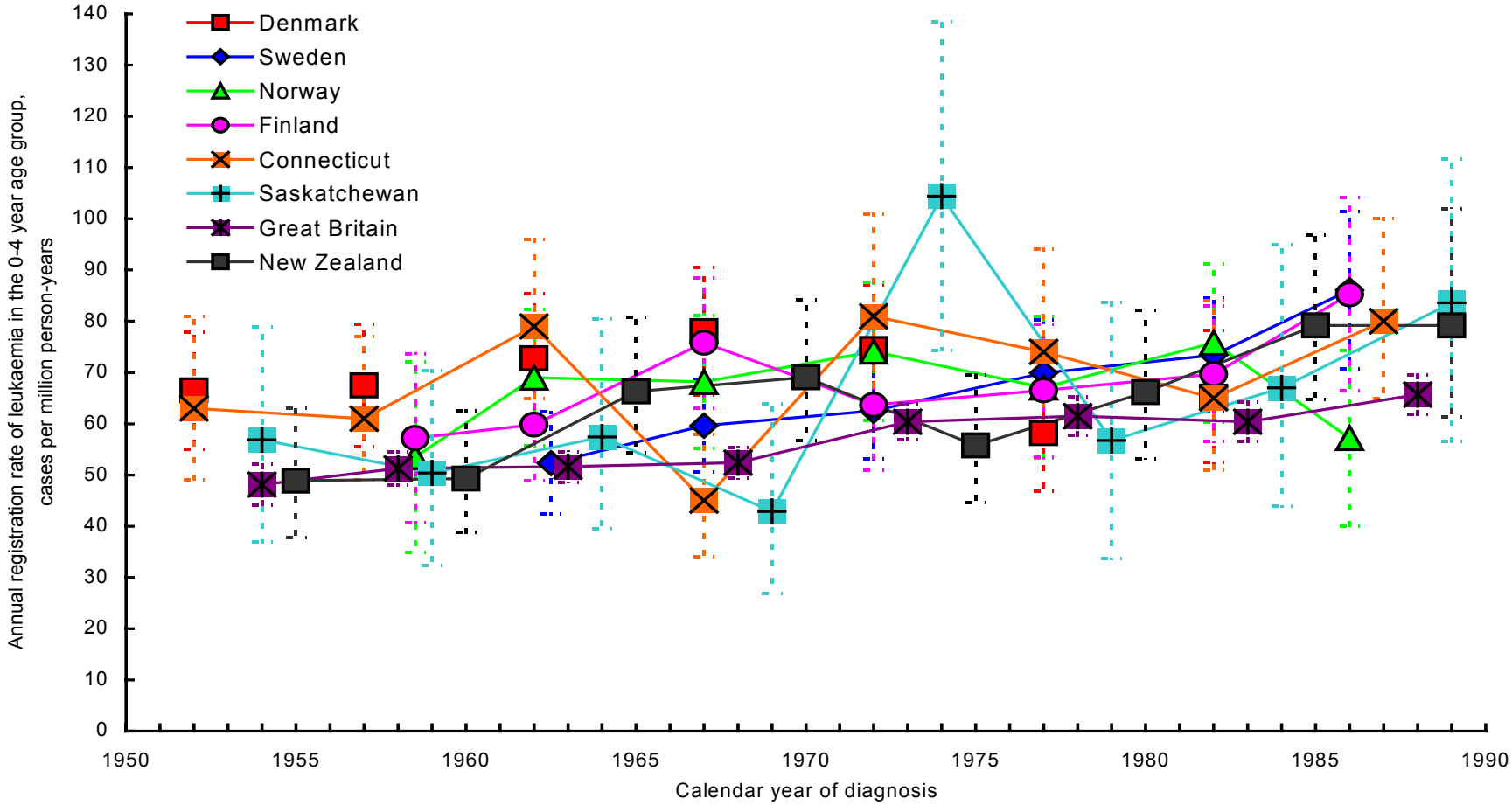

Figure 4B.2 Incidence rate of all leukaemias among children aged 0–4 years, 1950–1990. Incidence data from eight cancer registries. Error bars show 95% confidence intervals on rates

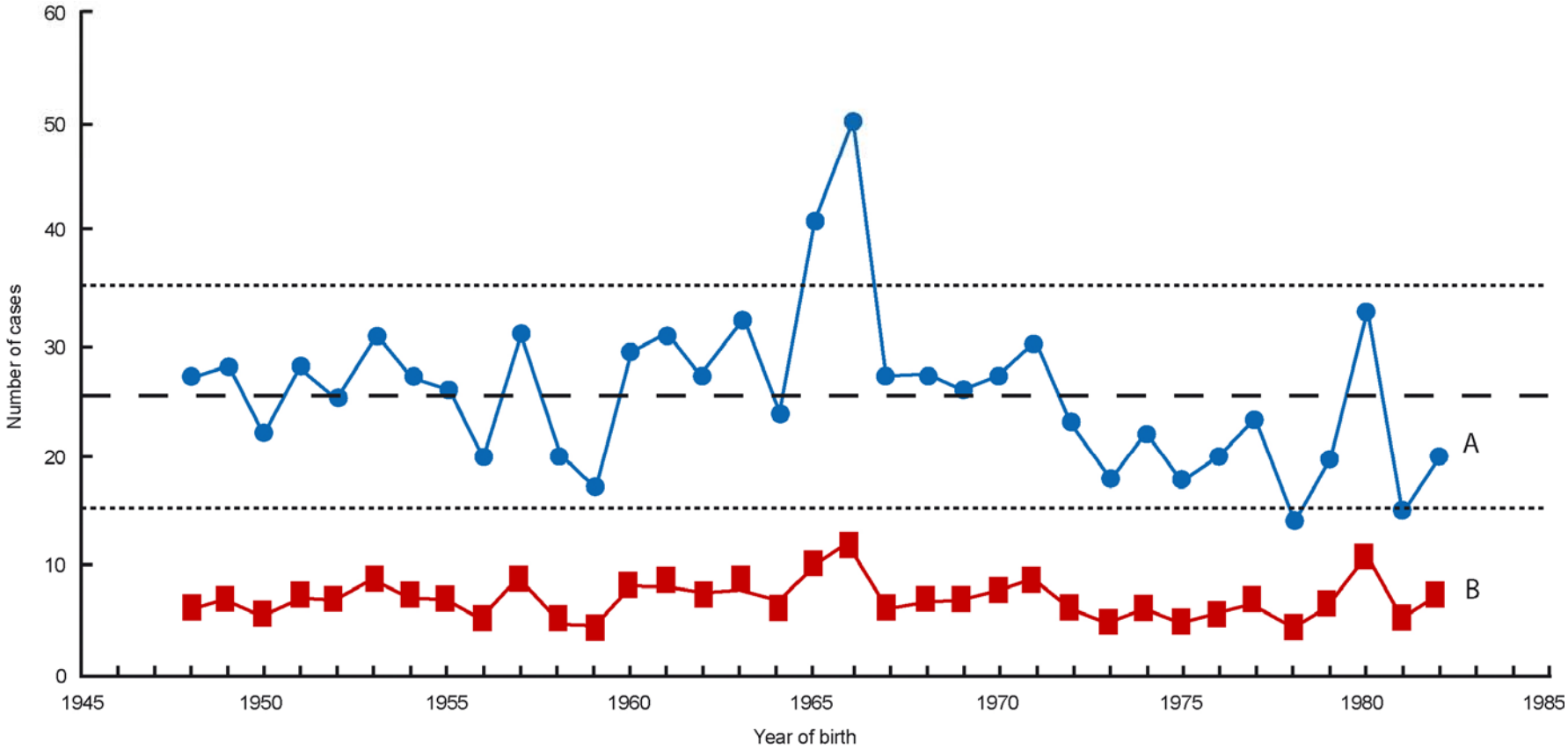

Figure 4B.3 Leukaemia incidence in Denmark, ages 0–4 years, by year of birth. Line A shows the recorded number of cases by year of birth (the average, 26, ±2 x standard deviation are shown as dashed lines); line B shows the number of cases standardised to a population of 100,000

Table 4B.1 Classification of calendar years by bone marrow dose equivalent for fetus or 1 year old and by testis dose equivalent for adult, as used by Darby *et al* (1992)

Year	Classification for bone marrow dose	Classification for testis dose
1951	Low-1	Low-1
1952		
1953		
1954		
1955		Medium-1
1956		
1957	Medium-1	
1958		
1959		
1960		
1961		
1962	High	High
1963		
1964		
1965		
1966	Medium-2	Medium-2
1967		Low-2
1968		
1969		
1970		
1971		
1972	Low-2	
1973		
1974		
1975		
1976		
1977		
1978		
1979		

(6) Hakulinen *et al* (1986) presented information on infant leukaemia rates in the Nordic countries. In particular, rates of infant acute leukaemia in Denmark were higher in the 1960s and later than in earlier years. As noted earlier, this analysis excluded leukaemia registrations with type unknown. Figure 4B.4, based on data for leukaemia of all types as used by Darby *et al* (1992), indicates a raised rate of infant leukaemia not only during the period of peak fallout during the earlier 1960s but also later in the decade, after fallout levels had decreased. Data for the other Nordic countries do not show such trends in infant leukaemia rates; see Hakulinen *et al* (1986) and also Figure 4B.4, which shows infant leukaemia rates for each of Denmark, Norway, Finland and Sweden by year of diagnosis.

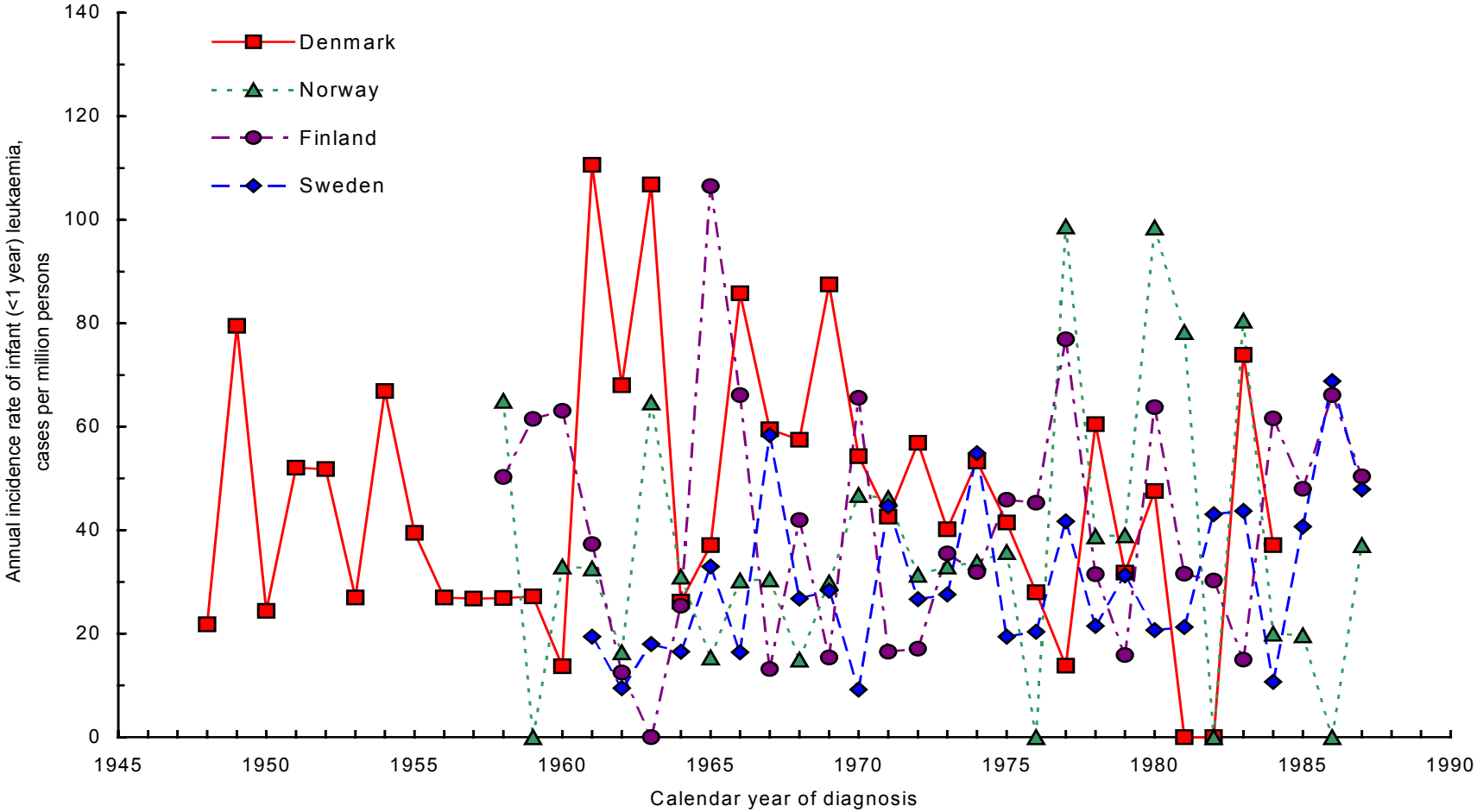

Figure 4B.4 Annual rate of incidence of all leukaemias among infants (<1 year of age) in Denmark, Norway, Finland and Sweden, by year of diagnosis, 1948–1987

Table 4B.2 Relative risk of childhood leukaemia incidence in Nordic countries for categories of exposure to weapons fallout

Relative risk of childhood leukaemia incidence in Nordic countries for categories of exposure to weapons fallout (see Table 4B.1), based on dose equivalent to the red bone marrow either after birth or to the fetus, or the dose equivalent to the father's testes in the year before birth. Values are standardised for age, gender and country (Darby *et al*, 1992).

Age (years)	Exposure category				
	Low-1 [a]	Medium-1	High	Medium-2	Low-2
Post-natal dose					
0–14	1.00	0.92	1.01	0.96	1.00
0–4	1.00	0.91	1.10	1.04	1.10
Fetal dose					
0–14	1.00	1.01	1.03	1.00	1.01
0–4	1.00	1.02	1.08	1.06	1.08
Paternal dose					
0–14	1.00	0.99	1.01	0.96	1.00
0–4	1.00	0.99	1.06	0.96	1.04

a Reference category.

USA

(7) Archer (1987) reported that childhood leukaemia mortality in the USA increased during and for several years after atmospheric nuclear weapons testing and decreased sharply thereafter. It should be noted that improvements in treatment during the latter period led to increases in cure rates for this disease. As shown in Figure 4B.2, data from long-running cancer registries in Connecticut ((Heston *et al*, 1986; Connecticut Tumor Registry, 2001; Polednak, 2001, 2003) and Saskatchewan, Canada (Wang and Haines, 1995), do not indicate the same type of decrease in leukaemia incidence rates in the 1970s as do the mortality data reported by Archer. However, the cancer registry data are sparser since they relate to smaller populations. Archer (1987) also noted that differences between states in US childhood leukaemia mortality correlated with a composite exposure index based on ^{90}Sr concentrations in food, cow's milk and human bone. Based on an estimated red bone marrow dose to children of 4.05 mGy from ^{90}Sr and ^{137}Cs, and an estimated increase of 9.5% in leukaemia mortality at ages 5–19 years during the peak fallout period, Archer estimated that leukaemia mortality was increased by 6.46 deaths per 10,000 persons per year per Gy. This value is similar to that predicted by the BEIR V Committee, based on Japanese A-bomb data (NRC, 1990). However, Archer's value may be an underestimate, owing to overestimation of fallout doses – perhaps by a factor of two, according to Simon *et al* (1995).

(8) Whereas most studies of leukaemia and weapons fallout have been based on aggregated data, Stevens *et al* (1990) conducted a case–control study of this topic in southwest Utah (USA), which received fallout from weapons testing at the Nevada Test Site. This involved individual assessments of doses to the bone marrow – mostly from external radiation, but also from internal exposures – both for persons who died of leukaemia and for a control group. For acute leukaemia deaths at ages less than 20 years prior to 1964, there was a statistically significant increasing trend in risk with bone marrow dose. In particular, the relative risk was estimated as 7.82 (95% CI 1.9, 32.2) for estimated doses in the range 6–30 mGy, based on five deaths in this upper dose category. The

central estimate of the trend in risk per unit dose was about twice that predicted using the BEIR V leukaemia risk model (NRC, 1990), although the 95% confidence interval for this estimate included the BEIR value.

Great Britain

(9) Haynes and Bentham (1995) analysed childhood leukaemia mortality from 1950 to 1967 and childhood leukaemia registrations from 1963 to 1987 in Great Britain in relation to patterns of fallout from weapons testing. Regions were classified as 'wet' or 'dry', based on rainfall records, as a means of classifying areas according to levels of fallout. In addition, calendar years of death or registration were used to assign post-natal exposures into categories ordered Low-1, Medium-1, High, Medium-2 and Low-2, in a manner similar to that used by Darby *et al* (1992). Table 4B.3 shows mortality and registration rates for wet and dry areas, by exposure period, and separately for ages 0–14 and 0–4 years. In most instances, leukaemia rates were higher in the dry areas than in the wet areas. At ages 0–14 years, the ratio of rates in the wet and dry areas was fairly uniform over time. At ages 0–4 years, the rate ratio for the high exposure period divided by the rate ratio for the two periods of medium exposure combined was 1.23 (p=0.008 for test for difference between the two rate ratios) when based on mortality data; the corresponding value based on registrations was 1.08 (p=0.31).

Table 4B.3 Leukaemia death and registration rates per 100,000 persons per year in wet and dry regions of Great Britain, based on post-natal dose equivalent to red bone marrow (Haynes and Bentham, 1995)

	Exposure category [a]				
	Low-1	**Medium-1**	**High**	**Medium-2**	**Low-2**
Age 0–14 years					
Deaths					
Wet rate	3.03 (1377) [b]	3.17 (945)	2.84 (1808)	2.13 (796)	1.62 (781)
Dry rate	3.48 (1537)	3.44 (1005)	3.12 (1940)	2.41 (903)	1.71 (846)
Rate ratio	0.87	0.92	0.91	0.88	0.95
Registrations [c]					
Wet rate			3.65 (2326)	3.60 (1344)	3.70 (1786)
Dry rate			3.97 (2472)	3.94 (1474)	3.77 (1870)
Rate ratio			0.92	0.91	0.98
Age 0–4 years					
Deaths					
Wet rate	4.20 (668)	3.98 (407)	3.67 (583)	2.45 (304)	1.61 (322)
Dry rate	4.83 (737)	4.59 (455)	3.55 (571)	3.10 (390)	1.74 (364)
Rate ratio	0.87	0.87	1.03	0.79	0.93
Registrations					
Wet rate			5.13 (815)	5.74 (713)	5.99 (1200)
Dry rate			5.18 (832)	6.25 (787)	6.15 (1289)
Rate ratio			0.99	0.92	0.97

a Categories as defined by Haynes and Bentham (see paragraph 9).

b Numbers of deaths and registrations are given in brackets.

c Registration data were not available prior to the period of peak fallout.

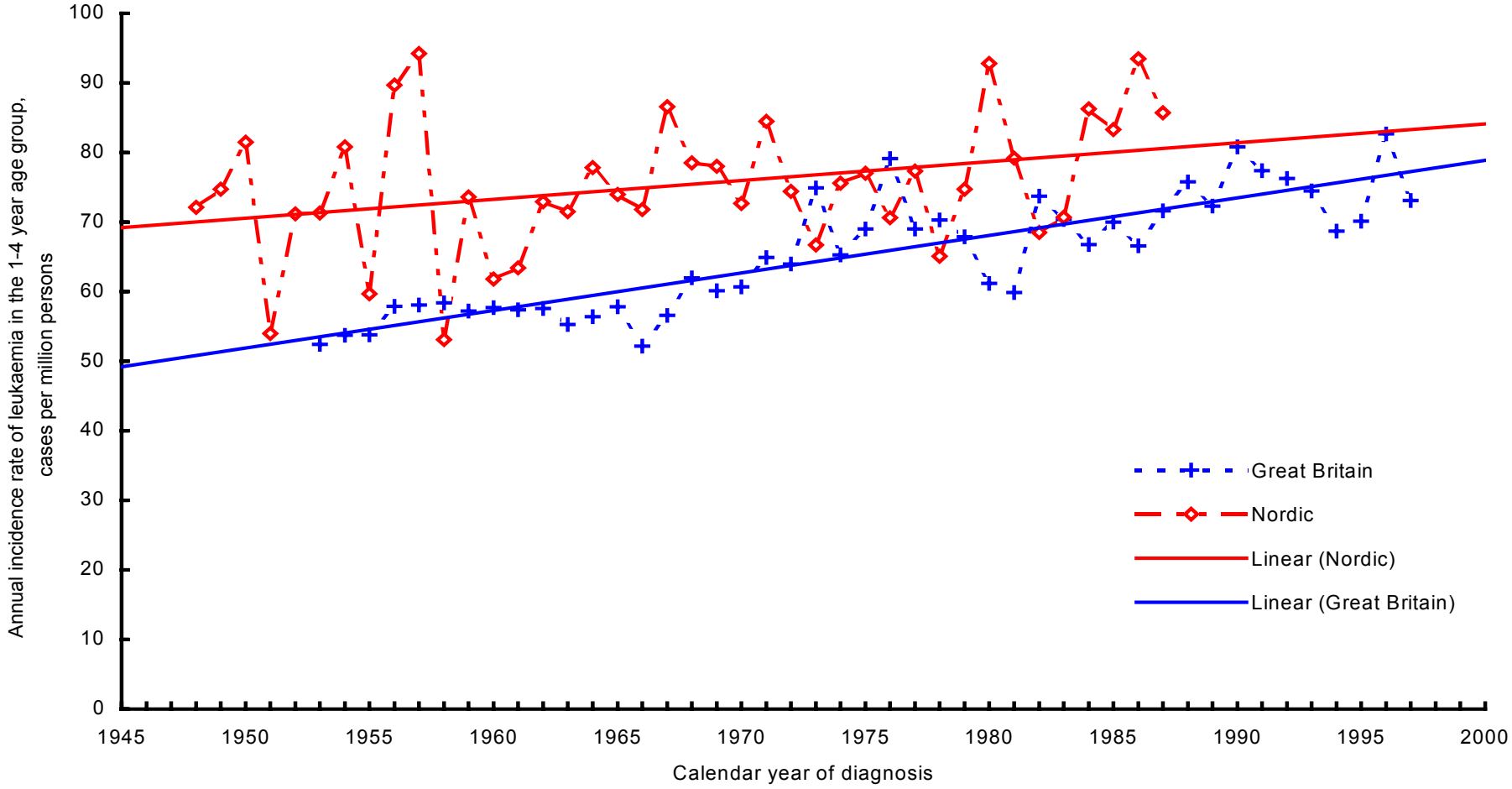

Figure 4B.5 Annual rate of incidence of all leukaemias among young children (1–4 years of age) in Great Britain and the Nordic countries, by year of diagnosis, 1948–1997. Solid lines show linear temporal trends of annual incidence rates

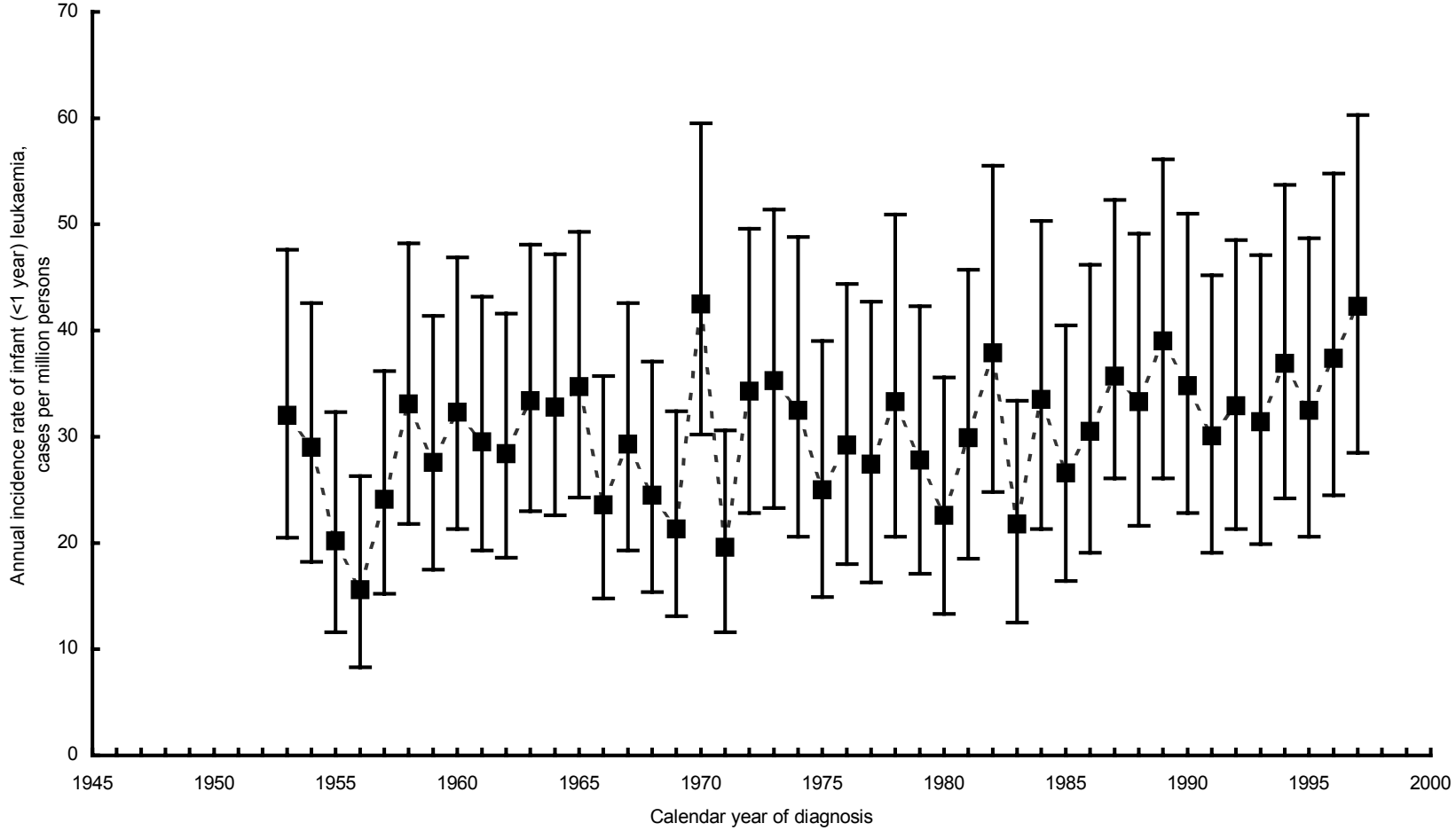

Figure 4B.6 Annual rate of incidence of all leukaemias among infants (<1 year of age) in Great Britain, by year of diagnosis, 1953–1997. Error bars show 95% confidence intervals on annual rates

(10) Data on childhood leukaemia incidence rates in Great Britain dating back to the 1950s were supplied to the Committee by the CCRG, for use in analysing trends in relation to fallout from atmospheric nuclear weapons testing. Figure 4B.2 shows rates at ages 0–4 years by 5-year periods of diagnosis, while Figure 4B.5 gives rates at ages 1–4 years for individual years of diagnosis over the period 1953–1997. These figures indicate long-term increases in leukaemia rates at these ages over a period of several decades. In particular, Figure 4B.5 shows that the rate of increase in Great Britain was greater than that in the Nordic countries over the same period. This finding is likely to have been influenced by higher levels of under-registration of leukaemia during the 1950s and 1960s in Great Britain, when compared with the Nordic countries where cancer registration started earlier. It would also complicate analysis of the British data along the lines performed by Darby *et al* (1992) using Nordic data. However, it is evident from Figure 4B.5 that there was no clear increase of leukaemia at ages 1–4 years either during or shortly after the period of peak weapons fallout.

(11) Figure 4B.6 shows rates of infant leukaemia in Great Britain over the period 1953–1997. In contrast to the findings for Denmark but in accord with the results for other Nordic countries highlighted above (see Figure 4B.4), no increase in British infant leukaemia rates is apparent during the period of peak weapons fallout. It should be noted that the levels of exposure in Denmark and Great Britain would have been similar.

ANNEX 4C
Epidemiological Studies of UK Coastal and Estuarine Areas

Studies around Nuclear Installations

(1) Rates of leukaemia and other cancers in young people living near Sellafield and Dounreay nuclear plants have been the subject of detailed investigations; see COMARE (1988, 1996, 1999a, 2002). Studies have also been conducted around various other UK nuclear installations situated on the coast or near estuaries. For example, Bithell *et al* (1994) examined rates of leukaemia and non-Hodgkin's lymphoma (NHL) during 1966–1987 at ages 0–14 years in the proximity of 23 nuclear installations in England and Wales, many of which were in coastal or estuarine locations. There was no evidence of an increase in leukaemia and NHL with 25 km of the sites, or of a general increase in rates with increasing proximity to the sites, as measured by a linear trend test. The only sites for which this trend test gave statistically significant results were Sellafield (on the coast of West Cumbria) and Burghfield (inland). A corresponding analysis for Scotland showed no evidence of a general increase of leukaemia and NHL years during 1968–1993 at ages 0–14 near nuclear sites there (Sharp *et al*, 1996). There were statistically significant increases within 25 km of Dounreay (observed/expected (O/E) = 1.99), Chapelcross (O/E = 1.08) and Rosyth (O/E = 1.02), all of which are located on the coast or near estuaries, although the linear test for trend in risk with proximity to the sites did not give statistically significant results.

(2) The above studies focused on proximity to nuclear installations specifically. Some other reports have focused on locations within the general vicinity of nuclear sites, such as mud flats.

Hinkley Point

(3) In reports by Green Audit, Busby *et al* (2000) concluded that there was a statistical significant excess of mortality from several types of cancer, including female breast cancer and prostate cancer, in the proximity of Hinkley Point nuclear power station in Somerset. In contrast to some other studies around nuclear installations, the focus of this analysis was not the power station itself but rather a point on mud flats, close to Burnham-on-Sea, around which concentric circles were drawn. The reason for selecting this precise location is not entirely clear. Furthermore, because of the high cure rate of breast cancer, the interpretation of findings for mortality is problematic. Busby *et al* (2000) reported a significant excess of breast cancer mortality in the ward of Burnham North, although there was no excess of breast cancer deaths in the other wards adjacent to the mud flats. In a subsequent Green Audit report, Busby and Rowe (2002) reported the results of a household survey of the Burnham North ward. The authors claimed that there were excesses of cancer of the breast, kidney and uterine cervix and of leukaemia associated with exposure to man-made radioactivity via the local estuarine sands, related to operations at Hinkley Point nuclear power station. However, a study by the South West Cancer Intelligence Service, described by COMARE (2003a), showed that the Green Audit study only covered a small sample of the cases arising in the ward. In contrast, the complete cancer registration data set for the ward the data showed no cancer excess, other than for leukaemia. When this excess of leukaemia cases was studied, the majority of the extra cases proved to be chronic lymphocytic leukaemia (CLL), a cancer not considered by previous investigators to be associated with exposure to radiation.

Bradwell

(4) Green Audit (Busby *et al*, 2001a, 2001b; Busby and Bramhall, 2002) and the Small Area Health Statistics Unit (SAHSU, 2001, 2002) have produced reports drawing conflicting conclusions about deaths from cancer, particularly breast and prostate cancer, around

Bradwell nuclear power station in Essex. Both groups used mortality data from the Office for National Statistics (ONS). The Green Audit reports have largely concentrated upon electoral wards adjacent to the tidal reaches of the River Blackwater (in contrast to the approach taken by Green Audit at Hinkley Point), whereas SAHSU adopted a concentric circle approach with the Bradwell power station at its centre. There were large differences in the figures presented in the first two reports from the two groups. Following investigations by ONS of these differences and examination of the Green Audit and SAHSU reports, COMARE (2003b) concluded that all three Green Audit reports contained errors in the actual numbers of deaths and erroneous or inappropriate figures for the expected numbers of deaths which, together with inappropriate comparisons of various areas, resulted in overestimation of the risks. Errors in the first SAHSU report, which underestimated the cancer risks, were corrected in the second report. COMARE (2003b) stated that analyses using correct mortality figures and the most appropriate expected values do not indicate any significant excess of cancer mortality around Bradwell, nor do they indicate any substantial or statistically significant risk of breast cancer mortality in groups of wards bordering the Blackwater estuary, or in Maldon compared with Burnham-on-Crouch.

Studies of Coastal and Estuarine Areas

(5) In addition to studies in the general vicinity of nuclear sites, analyses have been conducted of leukaemia rates in relation to proximity to coastal and estuarine areas in various parts of Great Britain.

Wales

(6) In a Green Audit report, Busby *et al* (1998) concluded that there was a significant excess of childhood leukaemia in North Wales associated with residential proximity to the coast. A separate study, carried out by Steward *et al* (1999) of the Welsh Cancer Intelligence and Surveillance Unit (WCISU), did not support this conclusion. After carrying out an independent check on the number of cases of childhood leukaemia in these Welsh counties, using data from the National Registry of Childhood Tumours, COMARE (1999b) stated that the data held by Green Audit, on which the analysis by Busby *et al* (1998) was based, were incorrect. These data were received from the Welsh Cancer Registry (WCR) in 1995. A further dataset was received from WCR in 1996 but was not used in the analysis by Busby *et al.* However, this second dataset did not show a significant excess of childhood leukaemia incidence when used with the analysis structure of Busby *et al* (1998). On the basis of the Steward *et al* data, COMARE (1999b) stated that it found no evidence to support the contention that there is an increased incidence of childhood leukaemia or other childhood cancers amongst the Welsh population living close to the Irish Sea.

(7) In the course of further investigations, COMARE (2001) attempted to distinguish between the errors of cancer registration generally, some problems known to have occurred at WCR and the very specific tabulation error that exists in the data file on which the analyses by Busby *et al* are based. That data file contains about twice the number of cases of leukaemia as those recorded by WCR and WCISU for the relevant period and, because these are concentrated in certain geographical areas, the report by Busby *et al* includes an even greater excess of cases. Whilst there are recognised errors in cancer registration arising from failure to ascertain cases or remove duplicates, incorrect diagnoses and incorrect location of cases, COMARE (2001) concluded that none of these errors could explain the findings of Busby *et al* (1998). Furthermore, the various other childhood leukaemia datasets considered by COMARE agree reasonably well, while that used in the Busby *et al* analyses is totally different and produces childhood leukaemia registration rates that are inconsistent with those presented in contemporaneous reports. COMARE (2001) concluded that the data used by Busby *et al* are incorrect, and reiterated its original conclusion that it had found no evidence to support the contention that there was an increased incidence of childhood leukaemia or other childhood cancers close to

the North Wales coast. Its conclusion was supported by a more complete analysis of the WCISU data by Steward and John (2001).

Leukaemia Research Fund Analyses

(8) Alexander *et al* (1990) carried out a study of leukaemia incidence in relation to social class and proximity to estuaries, using the data from the Leukaemia Research Fund (LRF) Data Collection Study (DCS) for the years 1984–1986. The geographical region examined, comprising 22 counties or part-counties that contributed reliable registration data to the DCS during the study period, is shown in Figure 4C.1. The study area and population data were based on electoral wards defined at the 1981 census. All leukaemia registrations, with the exception of chronic lymphocytic leukaemia (CLL, that has similarities to the lymphomas), were included in the study for the age group 0–84 years, older cases being excluded because of possible under-ascertainment. The childhood age group 0–14 years was examined separately.

(9) Alexander *et al* (1990) grouped wards into three classes: inland, coastal or estuarine. Inland wards were used to generate a reference registration rate against which the rates for estuarine and coastal wards were compared to obtain relative risks. Relative risks were adjusted for the possible confounding influences of social class, urban–rural status and the county of a ward. The results of the Alexander *et al* study are summarised in Table 4C.1.

Table 4C.1 Summary of results of the studies of Alexander *et al* (1990) and Lloyd *et al* (2002)

	Relative risks and 95% confidence intervals	
	Alexander *et al* (1990)	**Lloyd *et al* (2002)**
All leukaemias (except CLL)		
Inland	1.00 (reference)	1.00 (reference)
Coastal	0.83 (0.70, 0.98)	1.14 (1.01, 1.29)
Estuarine	1.09 (0.98, 1.22)	1.03 (0.94, 1.13)
Childhood leukaemias		
Inland	1.00 (reference)	1.00 (reference)
Coastal	0.69 (0.37, 1.29)	1.00 (0.72, 1.40)
Estuarine	1.20 (0.83, 1.72)	0.87 (0.69, 1.09)

(10) To test the hypothesis raised by Alexander *et al* (1990) of an increased incidence of leukaemia around estuaries, a subsequent study of data was conducted using a larger dataset from the LRF Data Collection Survey (Lloyd, 1999; Lloyd *et al*, 2002). The years 1987–1993 were chosen so that the analysis would be independent from the original study, and 1993 was the latest year where data collection from the DCS was complete. The areas of England and Wales that contributed data to the DCS changed again after 1988. Hence, Lloyd (1999) only had DCS data available from the two years 1987–1988 that covered exactly the same study area as that used by Alexander *et al* (1990) for the three years 1984–1986. For the period 1989–1993, there was still a substantial overlap with the area studied by Alexander *et al* (1990), but South and South West Wales, the East Midlands and East Suffolk left the DCS area and central Southern England joined it. Southwest England, Yorkshire, Cumbria and Lancashire continued to contribute data to the DCS throughout 1987–1993. Furthermore, since Lloyd *et al* (2002) used wards defined at the 1991 census rather than the 1981 census, slight differences exist between the common counties included in this study and that of Alexander *et al* (1990), owing to boundary changes. The status of the areas that contributed data to the study of Lloyd *et al* (2002) during 1987–1993 is shown in Figure 4C.1.

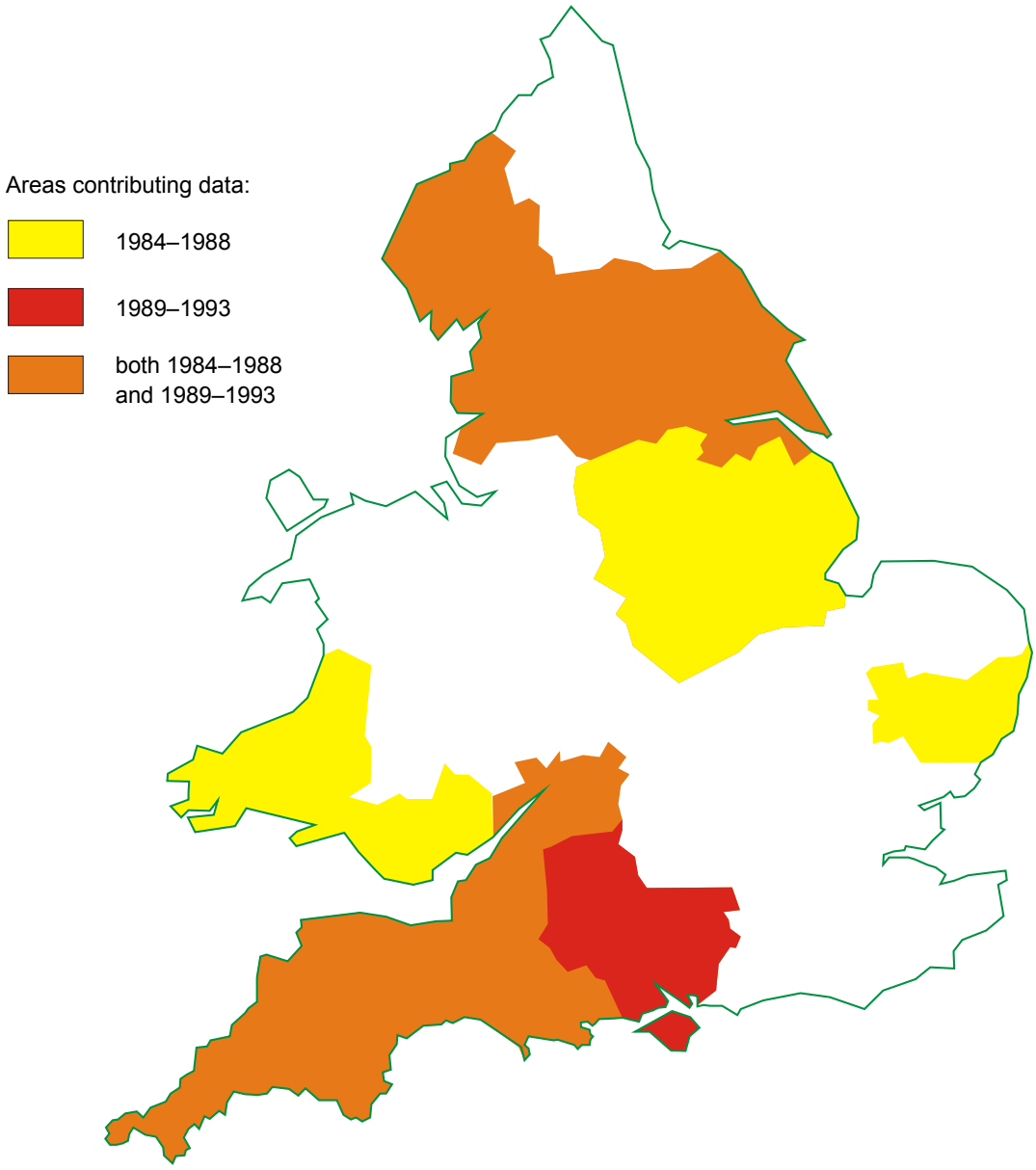

Figure 4C.1 Areas of England and Wales covered by the Leukaemia Research Fund (LRF) Data Collection Study during the ten years 1984–1993 (from Lloyd, 1999)

(11) Table 4C.1 shows results from the study by Lloyd *et al* (2002), alongside those of Alexander *et al* (1990). Lloyd *et al* (2002) calculated relative risks adjusted for age, sex, urban–rural status and social class. It should be borne in mind that the areas examined in the two studies are somewhat different and utilise a ward structure from different censuses. In addition, the age group studied by Alexander *et al* (1990) was 0–84 years, while in the Lloyd *et al* (2002) study it was 0–79 years. Overall, the Lloyd *et al* (2002) study includes about 25% more cases of all leukaemias in estuarine wards than the study of Alexander *et al* (1990), and about twice as many cases of childhood leukaemias.

(12) Whereas Alexander *et al* (1990) found a relative risk for leukaemias at ages 0–84 years in estuarine wards that was raised to a marginal level of statistical significance, there was little evidence of a raised incidence of leukaemia at ages 0–79 years in estuarine wards from the Lloyd *et al* (2002) study. Conversely, Lloyd *et al* (2002) found a marginally significantly raised relative risk at ages 0–79 years in coastal wards (although not for childhood leukaemias), while Alexander *et al* (1990) found a marginally significantly lowered relative risk in coastal wards at ages 0–84 years (reflected in a non-significant decrease in relative risk for childhood leukaemias). Consequently, there is no consistent pattern of results between these two studies, which were based on separate datasets. Lloyd *et al* (2002) concluded that they were unable to confirm the estuarine association postulated by Alexander *et al* (1990).

ANNEX 4D
Sir Austin Bradford Hill's Tests of Causality

Excerpt from Bradford Hill (1965) 'The Environment and Disease: Association or Causation?' Proceedings of the Royal Society of Medicine, ***58,*** *295–300.*

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"Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of an association should be considered before deciding that the most likely interpretation of it is causation?

(1) Strength First upon my list I would put the strength of the association. To take a very old example, by comparing the occupations of patients with scrotal cancer with the occupations of patients presenting with other diseases. Percival Pott could reach a correct conclusion because of the *enormous* increase of scrotal cancer in the chimney sweeps. "Even as late as the second decade of the twentieth century", writes Richard Doll (1964), "the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed to tar or mineral oils and in the eighteenth century the relative difference is likely to have been much greater." To take a more modern and more general example upon which I have now reflected for over fifteen years, prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times as great. On the other hand the death rate from coronary thrombosis in smokers is no more than twice, possibly less, the death rate in non-smokers. Though there is good evidence to support causation it is surely much easier in this case to think of some features of life that may go hand-in-hand with smoking – features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess in cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable. If we cannot detect it or reasonably infer a specific one, then in such circumstances I think we are reasonably entitled to reject the vague contention of the armchair critic "you can't prove it, there may be such a feature".

Certainly in this situation I would reject the argument sometimes advanced that what matters is the absolute difference between the death rates of our various groups and not the ratio of one to other. That depends upon what we want to know. If we want to know how many extra deaths from cancer of the lung will take place through smoking (ie presuming causation), then obviously we must use the 'absolute differences between the death rates – 0.07 per 1,000 per year in non-smoking doctors, 0.51 in those smoking 1–14 cigarettes daily, 1.39 for 15–24 cigarettes daily and 2.27 for 25 or more daily. But it does not follow here, or in more specifically occupational problems, that this best measure of the effect upon mortality is also the best measure in relation to aetiology. In this respect the ratios of 8, 20 and 32 to 1 are far more informative. It does not, of course, follow that the differences revealed by ratios are of any practical importance. Maybe they are, maybe they are not; but that is another point altogether.

We may recall John Snow's classic analysis of the opening weeks of the cholera epidemic of 1854 (Snow, 1855). The death rate that he recorded in the customers supplied with the grossly polluted water of the Southwark and Vauxhall Company was in truth quite low – 71 deaths in each 10,000 houses. What stands out vividly is the fact that the small rate is

14 times the figure of 5 deaths per 10,000 houses supplied with the sewage-free water of the rival Lambeth Company. In thus putting emphasis upon the strength of an association we must, nevertheless, look at the obverse of the coin. We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so. Relatively few persons harbouring the meningococcus fall sick of meningococcal meningitis. Relatively few persons occupationally exposed to rat's urine contract Weil's disease.

(2) Consistency Next on my list of features to be specially considered I would place the *consistency* of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?

This requirement may be of special importance for those rare hazards singled out in the Section's terms of reference. With many alert minds at work in industry today many an environmental association may be thrown up. Some of them on the customary tests of statistical significance will appear to be unlikely to be due to chance. Nevertheless whether chance is the explanation or whether a true hazard has been revealed may sometimes be answered only by a repetition of the circumstances and the observations.

Returning to my more general example, the Advisory Committee to the Surgeon-General of the United States Public Health Service found the association of smoking with cancer of the lung in 29 retrospective and 7 prospective inquiries (US Department of Health, Education & Welfare, 1964). The lesson here is that broadly the same answer has been reached in quite a wide variety of situations and techniques. In other words we can justifiably infer that the association is not due to some constant error or fallacy that permeates every inquiry. And we have indeed to be on our guard against that.

Take, for instance, an example given by Heady (1958). Patients admitted to hospital for operation for peptic ulcer are questioned about recent domestic anxieties or crises that may have precipitated the acute illness. As controls, patients admitted for operation for a simple hernia are similarly quizzed. But, as Heady points out, the two groups may not be *in pari materia*. If your wife ran off with the lodger last week you still have to take your perforated ulcer to hospital without delay. But with a hernia you might prefer to stay at home for a while – to mourn (or celebrate) the event. No number of exact repetitions would remove or necessarily reveal that fallacy.

We have, therefore, the somewhat paradoxical position that the different results of a different inquiry certainly cannot be held to refute the original evidence; yet the same results precisely the same form of inquiry will not invariably greatly strengthen the original evidence. I would myself put a good deal of weight upon similar results reached in quite different ways, eg prospectively and retrospectively.

Once again looking at the obverse of the coin there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions. The experience of the nickel refiners of South Wales is an outstanding example. I quote from the Alfred Watson Memorial Lecture that I gave in 1962 to the Institute of Actuaries:

> "The population at risk, workers and pensioners, numbered about 1,000. During the ten years 1929 to 1938, 16 of them had died from cancer of the lung, 11 of them had died from cancer of the nasal sinuses. At the age specific death rates of England and Wales at that time, one might have anticipated 1 death from cancer of the lung (to compare with the 16), and a fraction of a death from cancer of the nose (to compare with the 11). In all other bodily sites cancer had appeared on the death certificate 11 times and one would have expected it to do so 10–11 times. There had been 67 deaths from all other causes of mortality and over the ten years' period 72 would

> have been expected at the national death rates. Finally, division of the population at risk in relation to their jobs showed that the excess of cancer of the lung and nose had fallen wholly upon the workers employed in the chemical processes.
>
> "More recently my colleague, Dr Richard Doll, has brought this story a stage further. In the nine years 1948 to 1956 there had been, he found, 48 deaths from cancer of the lung and 13 deaths from cancer of the nose. He assessed the numbers expected at normal rates of mortality as, respectively 10 and 0.1.
>
> "In 1923, long before any special hazard had been recognized, certain changes in the refinery took place. No case of cancer of the nose has been observed in any man who first entered the works after that year, and in these men there has been no excess of cancer of the lung. In other words, the excess in both sites is uniquely a feature in men who entered the refinery in, roughly, the first 23 years of the present century.
>
> "No causal agent of these neoplasms has been identified. Until recently no animal experimentation had given any due or any support to this wholly statistical evidence. Yet I wonder if any of us would hesitate to accept it as proof of a grave industrial hazard? (Hill, 1962)."

In relation to my present discussion I know of no parallel investigation. We have (or certainly had) to make up our minds on a unique event; and there is no difficulty in doing so.

(3) Specificity One reason, needless to say, is the specificity of the association, the third characteristic which invariably we must consider. If, as here, the association is limited to specific worker and to particular mites and types of disease an there is no association between the work and other modes of dying, then clearly that is a strong argument in favour of causation.

We must not, however, overemphasise the importance of the characteristic. Even in my present example there is a cause and effect relationship with two different sites of cancer – the lung and the nose. Milk as a carrier of infection and, in that sense, the cause of disease can produce such a disparate galaxy as scarlet fever, diphtheria, tuberculosis, undulant fever, sore throat, dysentery and typhoid fever. Before the discovery of the underlying factor, the bacterial origin of disease, harm would have been done by pushing too firmly the need for specificity as necessary feature before convicting the dairy.

Coming to modern times the prospective investigations of smoking and cancer of the lung have been criticised for not showing specificity – in other words the death rate of smokers higher than the death rate of non-smokers from many causes of death (though in fact the results of Doll and Hill, 1964, do not show that). But here surely one must return to my first characteristic the strength of the association. If other causes of death are raised 10, 20 or even 50% in smoke whereas cancer of the lung is raised 900–1,000% we have specificity – a specificity in the magnitude of the association.

We must also keep in mind that diseases may have more than one cause. It has always been possible to acquire a cancer of the scrotum without sweeping chimneys or taking to mule-spinning in Lancashire (Hill, 1930). One-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation though possibly if we knew all the answers we might get back to a single factor.

In short, if specificity exists we may be able draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily sitting irresolutely on the fence.

(4) Temporality My fourth characteristic is the temporal relationship of the association – which is the cart and which the horse? This is a question which might be particularly relevant with disease of slow development. Does a particular diet lead to disease or do the early stages of the disease lead to those peculiar dietetic habits? Does particular occupation or occupational environment promote infection by the tubercle bacillus or are the men and women who select that kind of work more liable to contract tuberculosis whatever the environment – or, indeed, have they already contracted it? This temporal problem may not arise often but it certainly needs to be remembered, particularly with selective factors at work in industry.

(5) Biological gradient Fifthly, if the association is one which can reveal a biological gradient, or dose–response curve, then we should look most carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers. That comparison would be weakened, though not necessarily destroyed, if it depended upon, say, a much heavier death rate in light smokers and a lower rate in heavier smokers. We should then need to envisage some much more complex relationship to satisfy the cause-and-effect hypothesis. The clear dose–response curve admits of a simple explanation and obviously puts the case in a dearer light.

The same would clearly be true of an alleged dust hazard in industry. The dustier the environment the greater the incidence of disease we would expect to see. Often the difficulty is to secure some satisfactory quantitative measure of the environment which will permit us to explore this dose–response. But we should invariably seek it.

(6) Plausibility It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.

To quote again from my Alfred Watson Memorial Lecture (Hill, 1962), there was

> "... no biological knowledge to support (or to refute) Pott's observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19th that led a prize essayist writing on the value and the fallacy of statistics to conclude, amongst other 'absurd' associations, that at could be no more ridiculous for the stranger who passed the night in the steerage of an emigrant ship to ascribe the typhus, which be there contracted, to the vermin with which bodies of the sick might be infected. And coming to nearer times, in the 20th century there was no biological knowledge to support the evidence against rubella."

In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Holmes advised Dr Watson, "when you have eliminated the impossible, whatever remains, *however improbable*, must be the truth".

(7) Coherence On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease – in the expression of the Advisory Committee to the Surgeon-General it should have coherence.

Thus in the discussion of lung cancer the Committee finds its association with cigarette smoking coherent with the temporal rise that has taken place in the two variables over the last generation and with the sex difference in mortality – features that might well apply in an occupational problem. The known urban/rural ratio of lung cancer mortality does not detract from coherence, nor the restriction of the effect to the lung.

Personally, I regard as greatly contributing to coherence the histopathological evidence from the bronchial epithelium of smokers and the isolation from cigarette smoke of factors carcinogenic for the skin of laboratory animals. Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agent, the lack of such evidence cannot nullify the epidemiological observations in man. Arsenic can undoubtedly cause cancer of the skin in man but it has never been possible to demonstrate such an effect on any other animal. In a wider field, John Snow's epidemiological observations on the conveyance of cholera by the water from the Broad Street pump would have been put almost beyond dispute if Robert Koch had been then around to isolate the vibrio from the baby's nappies, the well itself and the gentleman in delicate health from Brighton. Yet the fact that Koch's work was to be awaited another 30 years did not really weaken the epidemiological case though it made it more difficult to establish against the criticisms of the day – both just and unjust.

(8) Experiment Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed.

(9) Analogy In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy.

Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?

Tests of Significance

No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis."

ANNEX 4E
P-values and Confidence Intervals

(1) Epidemiological results are almost always subject, to some degree, to random uncertainties. To deal appropriately with the effects of such uncertainties epidemiology relies heavily upon the methods of statistical inference. Random uncertainty must always be borne in mind when interpreting the associations produced by epidemiological studies.

(2) The statistical significance ('p-value') attached to an epidemiological association is the probability that the result that was actually observed, or a more extreme result, would have been generated by the 'null hypothesis' (usually the hypothesis that there is no underlying effect of the factor under consideration). The smaller the p-value, the more unlikely it is that the finding would have arisen if the null hypothesis were, in fact, true. Many researchers consider a result 'statistically significant' if $p<0.05$, ie the null hypothesis would have produced the observed, or a more extreme, result less than 5% of the time, although there is no hard and fast rule about this 0.05 level.

(3) A related statistical measure is the confidence interval. A 95% confidence interval will contain the underlying value being estimated 95% of the time. The wider the confidence interval the less precise is the estimate, a reflection of the statistical power of the study. The confidence interval and the p-value are often presented together, particularly when a result is statistically significant, the p-value indicating just how strong is the deviation from expectation under the null hypothesis. However, the context of the statistical test must always be considered: an exploratory study in which many statistical comparisons are conducted will often generate results that are apparently 'statistically significant' just because the many tests performed increase the chance of producing uncommon deviations from expectation. Great care needs to be exercised in the interpretation of studies where multiple testing has been carried out.

(4) Just because an association is statistically significant does not mean that an underlying cause-and-effect relationship exists. It just means that the finding should be given additional attention to determine whether bias or confounding (or, indeed, chance) could be responsible, or whether the result does reflect a causal relationship. Hence, the interpretational guidelines set out, for example, by Sir Austin Bradford Hill which are reproduced above in Annex 4D. As a corollary, a result that is not statistically significant does not necessarily imply that no effect exists. Low statistical power, as indicated by a wide confidence interval, could well be responsible for an underlying effect not being detected, the deviation from expectation lying within the confidence interval. As a consequence, epidemiological results need to be considered in the context of the broad range of scientific evidence.

(5) The chosen level of statistical significance, or the chosen width of a confidence interval, is selected to strike a balance between 'false positive' results (ie a 'statistically significant' result produced by the null hypothesis) and 'false negative' results (when the null hypothesis is incorrect, but the statistical test produces a 'statistically non-significant' result). The 0.05 significance level is selected so that a correct null hypothesis will be rejected only 5% of the time. A reduction in the chosen level of significance will reduce the frequency with which a correct null hypothesis is rejected, but it will also increase the frequency with which an incorrect null hypothesis is accepted. This is because one is demanding a more pronounced deviation from expectation before rejecting the null hypothesis. On the other hand, an increase in the chosen level of statistical significance will reduce the frequency with which an incorrect null hypothesis is accepted, but will increase the frequency with which a correct null hypothesis is rejected. It is a question of balance between these two undesirable, but inevitable, features of statistical inference. A

prior calculation of the statistical power of a study (the probability of the study detecting a genuine effect of a given size at a given level of statistical significance) can allow a more appropriate balance between the frequency levels of 'false positives' and 'false negatives' because the probability of obtaining a 'false negative' result from the study is better determined and a consequent level of statistical significance can be selected on a better informed basis. However, in the absence of such calculations, it is conventional to adopt the 0.05 significance level as a reasonable balance between 'false positive' and 'false negative' results.

(6) Overall, there is no simple way of determining what a 'statistically significant' epidemiological association might mean; the context of the result is all-important. One would inevitably place less weight upon a novel finding arising from an exploratory study making multiple comparisons than upon the result of a study specifically designed to test an epidemiological association for which there was prior evidence. In other words, 'statistically significant' epidemiological associations, even those with a small p-value, must be interpreted in the context of all the available scientific evidence, which is what Sir Austin Bradford Hill's guidelines are designed to do.

ANNEX 4F
Statistical Power

(1) The statistical power of an epidemiological study is the probability that the study will be able to detect a genuine effect of a particular magnitude at a given level of statistical significance. The greater the magnitude of the underlying effect (ie the larger the underlying proportional increase in the risk), the greater will be the power of a study of a given number of subjects. As the underlying proportional effect of the factor under study decreases in magnitude, the number of study subjects must increase by a factor that is approximately a function of n^2 (where n is the number of study subjects) to maintain the power of the study. So, to maximise statistical power a study should:

a consider a range of exposures that is as wide as possible, giving large proportional effects, to as large a number of individuals as possible, particularly at moderate and high exposures where the magnitude of the effect will be greatest, and

b follow the individuals over as long a period as possible, to capture most of the relevant cases.

(2) Power calculations should always be carried out during the design of a study to determine the chance that the study will achieve its objective. A study with high power can permit the specification of a low level of statistical significance with which to reject the null hypothesis (of no effect), thus reducing the chance of a false positive result while at the same time maintaining a low probability of obtaining a false negative result.

(3) It is not necessary (in general) to conduct power calculations once a study has been conducted and analysed, because the statistical precision of the study can be determined by inspection of confidence intervals for estimates derived from the analysis of the data. Estimates with wide confidence intervals reflect a lack of statistical power and contain little statistical information; that is, the results are compatible with a wide range of magnitude of underlying effect, often including no effect at all. Negative findings from studies with low statistical power should be treated with caution because of the very real possibility of false negative results. It is important not to confuse absence of evidence in favour of an effect with evidence that an effect is absent. The width of the confidence interval associated with an estimated effect must be taken into account when assessing the magnitude of an underlying effect with which the estimate is compatible.

5 Conclusions

From Chapter 2 on Risks of Internal Emitters

1 Ionising radiations from internal and external sources generate similar physical and chemical interactions in living matter. The absence of fundamental differences between them suggests that their effects may be combined for radiological protection purposes. However, short-range charged particle emissions, both electrons (eg low energy beta particles) and alpha particles, are important contributors to internal but not external radiation exposures. The potential heterogeneity of energy deposition in tissues resulting from these internal emitters contrasts with the relatively uniform irradiation of tissues from most external sources and defines the central difference between these two sources of radiation exposure. The Committee agreed that a methodology for combining radiation effects from both types of source should, in principle, be achievable. However, the Committee was more divided on the adequacy of methods used to take account of such heterogeneity, and these matters have been a central issue addressed by the Committee.

2 The chemical properties of an element determine its distribution and retention in body tissues and cells and hence determine the extent to which it may be located in a way that short-range emissions may have an accentuated effect in terms of damage caused to cellular targets for the induction of cancer and genetic effects. Biokinetic and dosimetric models are used to determine this relationship between the distribution of radionuclides and targets cells. In some cases, simple models suffice because the element and its radioisotopes are known to be uniformly distributed in body tissues and the pattern of energy deposition is similar to that resulting from external irradiation. In other cases, complex models are required to account for heterogeneous energy distribution within tissues, requiring knowledge of the location of the radionuclide at different times after intake and the location of target cells. Data available for model development are of variable quality – in some cases, particularly for some of the more important radionuclides, good information is available, including human data, but in other cases reliance is placed on sparse animal data. In all cases, there is little information on variability between individuals and within human populations. The Committee concluded that in general the combination of biokinetic and dosimetric models gave rise to reasonable estimates of central values, but with a widely variable uncertainty range. The Committee was more divided on the likely span of uncertainties for specific radionuclides and situations of exposure, but there was agreement that in some cases uncertainties could extend over at least an order of magnitude.

3 The location of radionuclides within tissues is particularly important for alpha particles that typically have a range of a few tens of μm (traversing a few cells) and for low energy electrons (eg beta particle emissions from tritium, range <10 μm, and from Auger electrons: see Annexes 2B and 2C). For these radionuclides, sub-cellular location is important, as location in the cell nucleus can increase carcinogenic potential while location in cytoplasm can decrease risk. On the basis of substantial experimental data, it is recognised that these radiation types can cause greater damage per unit energy deposition than sparsely ionising radiations, such as gamma rays, X-rays and higher energy electrons, because of the density of their ionisations within small tissue volumes. The understanding of these differences, in terms of three-dimensional track structure and consequent interactions with DNA and other molecules, is a key goal of microdosimetry.

4 The Committee was generally in agreement that this field of research is not yet far enough advanced for microdosimetric techniques to present viable alternatives to current risk-related radiation dosimetry. However, there was agreement that advances in

microdosimetry were likely to provide insights into the reliability of dose estimates and may provide complementary alternative approaches. The desirability of further research was emphasised.

5 The ICRP provides comprehensive information on radiation doses estimated to result from radionuclide intake by ingestion or inhalation. The ICRP publishes biokinetic and dosimetric models, and values of weighting factors, used to calculate quantities called equivalent and effective dose. While the models are used to give estimates of absorbed dose (Gy) to target organs, tissues, or regions within tissues, equivalent and effective dose (Sv) introduce effects-related weightings to take account of RBE (w_R) and individual tissue contributions to total risk or detriment from cancer and hereditary effects (w_T). The calculation of equivalent dose to individual tissues appears to be a simple and convenient way of combining doses from different radiation types to assess overall risk of specific cancers (or genetic effects). The further step of combining and weighting equivalent doses to give an overall whole-body or effective dose is convenient in allowing summation of all radiation exposures, internal and external, for comparison with limits for whole-body exposure. However, exclusive use of effective dose can conceal very different patterns of dose delivery from different radionuclides, both in the irradiation of specific tissues and the time-course of dose delivery. Effective doses provide no information on the likely incidence of cancer of specific types, only on the overall probability of cancer induction (ie with no distinction of type). The Committee noted, and felt that it should be more strongly emphasised, that the ICRP recommends reserving the use of effective dose for radiological protection purposes at doses below dose limits. For specific assessments, the ICRP recommends that it will sometimes be better to use absorbed dose and specific data relating to RBEs for the radiations concerned and risk factors. The Committee considered that the use of such specific information should apply when doses are or may be a significant proportion of dose limits, for retrospective dose assessments and for the interpretation of epidemiological data. The Committee further concluded that it was important that the scientific basis of the ICRP methodology should continue to be challenged, and that developments in microdosimetry and radiobiology should inform judgements on their reliability.

6 Dose limits, constraints, and indeed tissue weighting factors are based largely on risk estimates for radiation-induced cancer resulting from external gamma ray exposure of the Japanese populations of Hiroshima and Nagasaki. The applicability of these risk estimates to internal exposure from short-range charged particle emissions can reasonably be questioned, given the potential complexity of the steps involved in assessing internal dose and risk. Available human data that allow quantitative estimation of risks from internal radiations, for alpha particle emitters, provide a measure of support for the use of these risk estimates. Most Committee members agreed that there does not appear to be any indication, within the limitations of the data available and the overall uncertainties in the risk estimates, of fundamental differences between internal and external radiation that cannot in principle be accommodated through the use of appropriate parameters (eg RBE or kinetic factors) in physiological models. Some members did not accept this view, and considered that there are biophysical and biochemical mechanisms that result in an enhanced effectiveness of internal emitters over external radiation in specific instances that is not taken into account in current methodology. There was agreement that enhanced effectiveness may occur as a result of radionuclide binding to DNA, but most members considered that this was an issue specific to low energy beta emitters and Auger emitters.

7 Two members argued that such instances as those quoted above occurred largely with artificial as opposed to naturally occurring radionuclides. Furthermore, they suggested that because living organisms have evolved in the presence of natural radionuclides the organisms would have adapted to their presence, which will clearly not be the case for the range of artificial radionuclides. For these reasons, these members felt

that artificial radionuclides, as a class, were likely to present an enhanced risk. However, the other members of the Committee did not concur with this view.

8 Committee members agreed that insufficient attention has been paid in the past to uncertainties in dose and risk estimates for internal emitters. Reliable quantitative estimates of uncertainties in dose coefficients for a range of radionuclides are not yet available. Uncertainties in estimating equivalent dose, which combines the uncertainties in estimating both absorbed dose and RBE, are always likely to be significant, and probably vary in magnitude from around a factor of 2 or 3 above and below the central estimate in the most favourable cases (ie where good data were available) to well over a factor of 10 in unfavourable ones (ie where they were not). For effective doses, there are additional uncertainties in the use of tissue weighting factors. Further work is required to quantify uncertainties in dose estimates for important radionuclides, with transparent identification of all the underlying contributions to overall uncertainties and how to compound them. The Committee concluded that it was important that doses and risks from internal emitters should be calculated on the basis of best current information, using central values, and with no bias towards 'conservatism' or 'pessimism' (as is sometimes implied). Introduction of such subjective considerations had no place in an objective assessment. The Committee agreed that, where appropriate, dose and risk estimates should be combined with an appreciation and explicit statement of the uncertainties involved. This approach would help identify those situations in which a precautionary approach might be appropriate, and was greatly to be preferred over one in which conservative/pessimistic estimates were arbitrarily introduced at various stages in the calculation.

From Annex 2B on Tritium

9 The Committee accepted that there was much evidence from radiobiology theory and from RBE experiments that tritium's RBE was greater than 1. Considering all observed effects of HTO exposure, RBE values were in the range of 1–3.5. For comparisons with gamma rays, most values were from 1–3; while for comparisons with X-rays, most values were from 1–2, with values of 1–1.5 predominating. These measured RBEs for tritium beta irradiation are reasonably consistent with estimates based on microdosimetric considerations. Some Committee members referred to studies of carcinogenesis in animals as being most relevant to the estimation of tritium RBE for cancer induction in humans. Studies of mammary tumorigenesis and acute myeloid leukaemia in mice had resulted in values of about 1 compared with X-rays (Gragtams *et al*, 1984; Johnson *et al*, 1995). Members differed in their views on the implications of tritium RBE data for the use of w_R in ICRP calculations of equivalent doses from tritium. Some supported the use by the ICRP of a single w_R value of 1 for all low LET radiations for general radiological protection purposes, while others considered that the ICRP should routinely apply a w_R of 2 or greater to tritium beta emissions.

10 Some Committee members considered that factors additional to RBE have been neglected in ICRP models for tritium and current dose coefficients may be underestimates by a factor of about 10. Those members who had contributed to the ECRR (2003) report pointed to w_R values for tritium of 10–30 (see text of Chapter 2). Other members concluded that ICRP dose coefficients for HTO were not substantial underestimates, but noted that values for OBT must be used with caution since they may well not apply to specific materials.

11 Several Committee members concluded that risks from tritiated DNA precursors were reasonably well understood on the basis of reliable experimental data, but others disagreed. Some members expressed concern about the possibility of environmental concentration of tritium contained in specific stable organic compounds and the potential for high RBE of tritium incorporated into DNA. A number of members considered that more research should be carried out on tritium microdosimetry.

From Annex 2C on Auger Emitters

12 Committee members were agreed that the possibility of increased risk from Auger emitters on the basis of cellular location and non-uniform distribution between cells within tissues should be examined for individual radionuclides and chemical forms of concern. This would involve experimental studies of distribution, together with studies of biological effects for those radionuclides/chemical forms showing significant presence in cell nuclei. The ICRP recognises these uncertainties for Auger emitters and has stated (ICRP, 2003) that they represent a special case and will need continued special attention.

From Annex 2D on Alpha Emitters

13 There was no consensus among members on the risks posed by localised 'hot' particle irradiation. Some members considered that particles with a particular content of an alpha emitter ('warm' particles) must be more hazardous than more uniform distribution of the same activity. Others were not persuaded by this argument.

14 Committee members agreed that the available data on the behaviour of radioactive particulates in the body do not support the proposal that they transfer readily to the fetus and pose a high risk of *in utero* leukemogenesis. However, the extent of possible risk was not agreed. It was also noted that the ICRP model of the respiratory tract was deficient in not taking account of the recognised lymphatic movement of particles to the general circulation.

From Chapter 3 on Biological Evidence

15 The views of the Committee were divided on many interpretational aspects of the biological data considered in Chapter 3. On induced genomic instability, bystander effects, minisatellite mutation induction and specific issues of microdosimetry, there was general agreement that many of the phenomena were real and some may well be an integral part of cellular and tissue response. There was, however, substantial disagreement as to whether the available data are sufficient to draw firm conclusions on the implications for radiation-induced health effects. A minority of the Committee held the view that the data clearly provided a major challenge to current estimates of low dose health effects and these members emphasised the implications for internal emitters. Other members were less persuaded on the scientific strength of the case. Many of these members believed that considerably more knowledge was needed and some considered that current epidemiological measures of risk were likely to incorporate contributions from these novel cellular responses, albeit with some low dose/low dose rate uncertainties.

16 On the second event theory, 'hot' particle theory, biphasic responses and artificial versus natural radionuclides**,** two members considered that, together, these theories meant that current ICRP risk models were very inaccurate and could underestimate the true level of radiation risks by 2 to 3 orders of magnitude or more. About a third of the Committee disagreed with these theories and with the view that the ICRP risks were greatly inaccurate. Another third also disagreed with the above theories, but considered that current radiation risks might still be seriously underestimated, in some cases, though for different reasons, see below and Chapter 2.

17 Almost half of the members were of the view that the biological evidence on these mechanisms was not adequately reflected in current ICRP models. Current risks could therefore be underestimated, at least to some degree, and perhaps significantly for some nuclides. These members considered it was possible that these underestimates could account for some epidemiological findings, especially at Seascale where COMARE had concluded that the observed leukaemia incidence would require radiation risks to be about 200- to 300-fold greater than those estimated by the NRPB. These members pointed out

that these biological mechanisms could act together (ie be multiplied), rather than separately (ie be added), to enhance risks to levels required to explain observed increases in risks.

18 The remaining members of the Committee were unsure of the implications. Of these, some were inclined to the view that risks were adequately taken into account in current models and epidemiological observations, and some to the view that more evidence was required before significant changes were made in current risk estimates for internal emitters. These differences of view existed because of lack of knowledge, particularly for the effects of low doses of radiation in *in vivo* studies. Members were agreed that long-term research was needed on the implications of these mechanisms for radiation risks, from both internal and external radiation.

19 Although there was not lengthy discussion of the issue, the majority of the Committee did not hold the view that a dose threshold was a general feature of radiation cancer risk, ie no risk at low doses. Some members agreed, however, that dose–response for cancer in some tissues was highly curvilinear and in specific circumstances an apparent dose threshold for risk might apply.

20 There was general agreement that new findings on radiation-induced bystander effects and radiation-induced genomic instability should continue to be included in consideration of health risks at low doses and their quantitative uncertainty. In this respect, the Committee recognised that the current ICRP recommendations, formulated in 1990, pre-dated much of the biological information discussed in Chapter 3. The Committee endorsed ongoing national and international radiobiology research programmes particularly in respect of microdosimetry, induced genomic instability, bystander effects, cancer mechanisms and germline minisatellite mutagenesis.

21 The Committee was not agreed on whether the biological evidence discussed in this chapter had immediate implications for radiological protection standards. A minority of the Committee considered that this was so and that Government should give consideration to the Precautionary Principle. Other members, whilst generally supportive of a precautionary approach to the interpretation of the science, did not share this view, principally because of their perception of a current lack of coherence in the experimental data and absence of clear links with health effects.

From Chapter 4 on Epidemiological Evidence

22 All members of the Committee believe that the epidemiological evidence is compelling for moderate and high levels of exposure to internally incorporated radionuclides producing a raised risk of adverse health effects in those exposed. All but one member of the Committee believe that the low level intake of radionuclides leads to some increased risk of adverse health effects as a result of the internal irradiation of organs and tissues. Some members think that the epidemiological evidence as a whole does not suggest that the predictions of current risk models are materially in error. Other members consider that these models may underestimate risks from intakes of certain radionuclides by relatively modest factors. Two members think that current models underestimate risks from intakes of radionuclides by very large factors. Conversely, one member thinks that any observed increases in risks at low doses are most likely to have causes other than radiation, ie current models overestimate risks at low doses. Consequently, there is little consensus amongst members on the epidemiological evidence as a whole.

23 The disagreements stem from differences of view about the appropriateness of the data and methodologies used in epidemiological studies and about interpretations of their findings. It is not anticipated that these can be resolved by further discussion. A core methodological concern is that the inherent limitations of epidemiological studies at low

levels of exposure make it difficult to reliably quantify health risks. Most of the Committee consider that the nature of the epidemiological evidence, taken as a whole, inevitably leads to uncertainties in current internal radiation risk models, although there are different views on the magnitude of these uncertainties. There is a consensus within the Committee that epidemiological evidence is strengthened when supplemented by laboratory and theoretical information on underlying mechanisms to guide estimates of risk at low doses.

24 The Committee has general and specific recommendations on future epidemiological studies (see Chapter 6). It is hoped that adherence to these recommendations may resolve disagreements in some areas. However, as indicated in paragraph 22, it seems likely that disagreements in other areas will remain for some years to come.

6 Recommendations

From Chapter 2 on Risks of Internal Emitters and Chapter 3 on Biological Evidence

1 The Committee recommends that the ICRP should give more explanation of the intended uses of equivalent dose and effective dose and their limitations when considering doses and risks from internal emitters. The ICRP (1991) has stated

> "For the estimation of the likely consequences of an exposure of a known population, it will sometimes be better to use absorbed dose and specific data relating to the relative biological effectiveness of the radiations concerned and the probability coefficients relating to the exposed population."

Committee members considered that this advice should be elaborated. In particular, it should be made clear that the use of specific information on exposures to internal emitters would be necessary in situations where doses may approach limits or constraints, in retrospective dose assessments and in the interpretation of epidemiological data.

2 The Committee noted that uncertainties in dose coefficients for some radionuclides are large and recommended that more work should be undertaken to quantify uncertainties for a range of internal emitters and to identify the major sources of these uncertainties. Information on uncertainties would inform judgements on the reliability of dose estimates and would also help identify research priorities which should then receive attention. Members encouraged COMARE to foster such analyses of uncertainties.

3 The Committee accepted that the use of absorbed dose, and dose quantities derived from it, as a measure of harm has fundamental scientific limitations which become progressively more important for charged particle emissions as their ranges decrease in cells and tissues. A particular concern was the adequacy of current models for the estimation of risks from short-range alpha, beta and Auger emitters as discussed in Chapter 2 and its annexes. The Committee concluded that research should be encouraged which was relevant to low level exposures to internal emitters and which addressed biological mechanisms and microdosimetric aspects. A number of members considered that more research should be carried out on tritium microdosimetry.

4 There was general agreement that new findings on the biological effects of radiation should continue to be included in consideration of health risks at low doses and their quantitative uncertainty. In this respect the Committee recognised that current recommendations from the ICRP, formulated in 1990, pre-dated much of the biological information discussed in Chapter 3. The Committee endorsed ongoing national and international radiobiology research programmes, particularly in respect of microdosimetry, induced genomic instability, bystander effects, cancer mechanisms and germline minisatellite mutagenesis. An important aspect was the reliability of the assumption of a linear no-threshold dose–response for effects at low doses.

5 The Committee recommends investigations of two specific issues.

a The complex whole-tissue responses to internally deposited radioactive particles of different sizes and activity levels, including those of intermediate activity, ie 'warm' particles. As discussed in Chapters 2 and 3, the available evidence, mostly for 'hot' particles, does not suggest that heterogeneity of dose delivery within tissues from short-range emitters in particles results in a substantial enhancement of cancer risks. However, some Committee members remained concerned that risks at low doses could be increased by local

delivery of dose from particles. They also considered that there was insufficient information on which to assess the possibility that inhaled particles might be transported to the fetus, although the available evidence suggests that the probability of particle transfer to the fetus is low, see Chapter 2.

b The possibility of enhanced effects from radionuclide binding to DNA, particularly in relation to ^{90}Sr. In the case of risks from ^{90}Sr, research requirements were delineated to address the question of whether a large fraction of a given ^{90}Sr intake might bind preferentially to chromosomes rather than being distributed homogeneously or being bound to non-cellular matrices. Specific investigations were recommended (see Chapter 3) to determine the binding of ^{90}Sr in chromosomes in human cell culture systems and analyse resulting chromosomal aberration yields. An *in vivo* study of cytogenetic damage in rodent bone marrow was also recommended.

From Chapter 4 on Epidemiological Studies

General Recommendations

6 The Committee recommends that all epidemiological studies should employ rigorous scientific methods, including the establishment of prior hypotheses, proper statistical analysis, and objective interpretation. In particular, the Committee supports the COMARE recommendation that organisations and research groups should establish scientific protocols and internal controls to prevent the errors mentioned in paragraph 71 of Chapter 4: these protocols and controls should be established before distributing data, conducting epidemiological analyses or publishing results.

7 In addition, the Committee recommends that epidemiological studies should be published in recognised peer-reviewed scientific publications. However, the Committee does recognise that the peer-review process may tend to reject evidence that does not conform to existing paradigms. Where epidemiological results are self-published, authors have a scientific and public responsibility to ensure that their analyses are carefully checked and closely examined prior to their publication by other scientists willing to check their work.

8 The Committee recommends that there should be much better communication between the various organisations that carry out epidemiological analyses. Indeed the Committee considers that there is scope for joint analyses by governmental and other organisations, including voluntary groups holding differing views on the question of radiation risks, and it recommends that steps be taken to explore the matter. However, it also notes that recent administrative provisions on ethical matters and data protection are making it difficult in practice to carry out epidemiological research: this merits careful consideration by the Government.

Specific Recommendations

9 The Committee recommends that groups of individuals exposed to radiation from internally deposited radionuclides should continue to be the subject of epidemiological studies. Suitable study groups for new or continuing studies include the following.

a **Nuclear industry workers** The Committee recommends that studies should be continued, and further evidence be obtained, on nuclear workers exposed to internal emitters in the UK, the rest of Europe (especially France), North America and the FSU. Assessments of the health status and organ-specific doses received by workers at the Mayak nuclear facility in the Southern Urals could lead to reliable risk coefficients for plutonium. In addition, consideration should be given to epidemiological studies of potential heritable effects among the offspring of workers at the Mayak facility, following parental exposures to internal emitters.

b **Residents near nuclear and other facilities** The Committee was unable to complete its proposed study of cancer incidence and mortality near the Bradwell nuclear facility due to lack of time. In view of this, it recommends that further epidemiological studies, using realistic methodological approaches, be considered in an attempt to resolve the question of whether cancer rates are generally higher in UK coastal and estuarine areas and in the vicinities of UK nuclear sites (see also next paragraph). Consideration should also be given to epidemiological studies of residents near the Techa River, contaminated by highly radioactive waste from the Mayak facility in Russia.

c **Patients and medical workers** The Committee recommends epidemiological studies of those exposed to internal emitters as a result of diagnostic investigations and therapeutic treatments.

d **Public exposures from fallout** Groups exposed in the FSU to the Chernobyl fallout in1986 should continue to be studied, particularly those who were heavily exposed when they were children. In addition, residents exposed to fallout from the Semipalatinsk nuclear weapons test site in Kazakhstan should be studied.

e **Residents and miners exposed to radon** The Committee welcomes the substantial efforts being expended in the study of groups exposed to radon.

10 Further to item (b) above, the Committee recommends further measurements of radioactivity levels in air, soil and other materials in coastal, estuarine and inland areas, to establish whether significant differences exist between these areas. In addition, the Committee is aware that the COMARE study of the geographical distribution of childhood cancer cases in Britain, particularly near nuclear sites, is nearing completion. When this study is finished, the results should be reviewed to determine whether they justify a broader study of adult cancers near nuclear sites and contaminated estuaries.

11 The Committee considers that bioassay techniques, to measure levels of radionuclides in study subjects, provide a valuable complement to epidemiological studies of those exposed to internal emitters. The Committee recommends that greater use be made of presently available bioassay techniques and that, in specific instances, the suitability of biodosimetry measurements on study subjects be assessed.

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Appendix A
Abbreviations and Acronyms

AAPM	American Association of Physicists in Medicine
ABCC	former Atomic Bomb Casualty Commission (now RERF qv)
AGIR	NRPB Advisory Group on Ionising Radiation
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
ANLL	acute non-lymphoblastic leukaemia
BEIR	(US) Committee on the Biological Effects of Ionizing Radiations
BMJ	British Medical Journal
BNFL	British Nuclear Fuels plc
Bq	becquerel
CCRG	Childhood Cancer Research Group
CERRIE	Committee Examining the Radiation Risks of Internal Emitters
CI	confidence interval
COMARE	Committee on Medical Aspects of Radiation in the Environment
DDREF	dose and dose rate effectiveness factor
DEFRA	Department of Environment, Food and Rural Affairs
DH	Department of Health
DNA	deoxyribonucleic acid
DoE	(US) Department of Energy
DTI	Department of Trade and Industry
EAR	excess absolute risk
EC	European Commission
ECLIS	European Childhood Leukaemia and Lymphoma Incidence Study
EPA	(US) Environmental Protection Agency
ERR	excess relative risk
ESTR	expanded simple tandem repeat
F_1	first generation offspring
F_2	second generation offspring
FoE	Friends of the Earth
FSA	Food Standards Agency
FSU	former Soviet Union
keV	kiloelectron volts
G_0	the resting state of the cell cycle
G_1	the first phase of the cell cycle
G_2	the third phase of the cell cycle

G_2/M	G_2 and the start of the mitotic phase of the cell cycle
Gy	gray
HTO	tritiated water
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
LET	linear energy transfer
LLRC	Low Level Radiation Campaign
LNT	linear no-threshold
LSS	Life Span Study
MAFF	former Ministry of Agriculture, Fisheries and Food (now within DEFRA qv)
mGy	milligray, one thousandth of a gray
MRC	Medical Research Council
mSv	millisievert, one thousandth of a sievert
NCRP	(US) National Council on Radiation Protection and Measurements
NGO	non-governmental organisation
NHL	non-Hodgkin's lymphoma
nm	nanometre, one billionth of a metre
NRC	(US) Nuclear Regulatory Commission
NRPB	National Radiological Protection Board
OBT	organically bound tritium
ONS	Office for National Statistics
OSCC	Oxford Survey of Childhood Cancers
PIAG	Patient Information Advisory Group
PPI	pre-parental irradiation
RBE	relative biological effectiveness
RERF	Radiation Effects Research Foundation
RR	relative risk
SAHSU	Small Area Health Statistics Unit
SET	second event theory
SIR	standardised incidence ratio
SMR	standardised mortality ratio
Sv	sievert
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
WHO	World Health Organization
μGy	microgray, one millionth of a gray
μm	micrometre, one millionth of a metre
μSv	microsievert, one millionth of a sievert

Appendix B
Report of CERRIE Workshop, July 2003

Topics for consideration at the Workshop were introduced by members of the Committee or the Secretariat, as indicated below. Their visual material is available on the Committee's website www.cerrie.org.

Monday 21 July, 2003

Session 1 Welcome and Introduction

The Chairman welcomed invitees to Oxford and introduced the CERRIE Workshop.

Session 2 Current Understandings of Radiation Risks

Dr Harrison set out the basis of current ICRP models for risk estimates for external and internal radiation; Dr Busby presented comments on the ICRP model; and Dr Fairlie described uncertainties in RBEs, biokinetic/metabolic models, and risk estimates.

In discussion, it was stated that the magnitude of uncertainties around central values of current risk estimates (in particular from the averaging of dose to tissue) should be identified and acknowledged. It was stated that, as regards the reliability of models, a problem was individual variability: for example, the highly variable barium excretion rates. Participants expressed sympathy with the Committee's concern over the microdosimetric aspects of current dose estimates. Other participants asked about the uncertainty ranges of present dose coefficients and queried whether the current ICRP risk coefficients were oversimplified or biased. On the Life Span Study of the A-bomb survivors, a speaker stated that the study had problems with dose reconstruction, cohorts and controls, and considered that its findings were only relevant to external, and not internal, exposures. He noted concerns re the LSS associated with: (1) the sex ratio of the exposed population; (2) suitability of the LSS control group; (3) Professor Alice Stewart's questions of the early deaths of susceptible populations prior to the setting up of the ABCC in 1950; (4) alteration of LSS data ie internal methodological inconsistencies; and (5) high external acute exposure risks used to determine low internal chronic exposure risks. On the other hand, others replied that the UNSCEAR recommendations on risk were conservative, although there were uncertainties about applying them across different populations. Views were also expressed in support of the ICRP approaches to the estimation of doses and risks from internal emitters. It was noted that this was not a static situation, but a continual process of improvement of models as more information became available.

In further discussion, some speakers expressed concern about the proposed removal by the ICRP of dose constraints and one said it would be disconcerting if this were in response to lobbying from the nuclear industry. Another stated that current risk models were deployed to counter claims of health effects found near nuclear plants; and another that recently the ICRP seemed to be unduly attentive to the views of the nuclear industry. The ICRP framework was regarded by others as essentially a socio-legal administrative convenience to protect nuclear workers: the public had little input into this framework.

On the other hand, it was stated that in the UK the real problem was limited to Seascale: if the effects were due to radioactive pollution alone then other parts of that region should show increased adverse health effects. Another speaker expressed concern that ICRP models were based on retrospective epidemiological studies: clearer data were needed to be able to calculate dose limits. The models were changing, and retrospective studies

should use individual data where possible in order to address individual genetic differences re sensitivity to radiation.

Others addressed the historical and social context of the debate: since certainty only followed after much human experience it would take a long time to resolve some of the questions the Committee was addressing. In the meantime, radiological protection measures should be continually reviewed. Another speaker noted that epidemiology was a blunt tool in view of the large numbers required to achieve statistical significance.

Session 3 Radiation Effects

Professor Wright reviewed radiation-induced genomic instability and bystander effects.

In discussion, various participants stated they had carried out studies that implied bystander effects *in vivo* as well as *in vitro*. A number of speakers queried the relationship between genomic instability, clearly a real effect, and background radiation. A speaker replied that, following a 1957 nuclear accident in Russia, studies in the then USSR had showed a 'genomic instability like wave' which was silent in the 1960s but which appeared in the 1970s. Speakers stated that quite different uncertainties existed as regards the risks from internal and external exposures, although others replied that existing ICRP data did not support this view.

Others emphasised the ethical conundrum associated with sub-population susceptibility to radiation, as much depended on the genetic make-ups of exposed individuals. Future human bystander assays were expected to provide answers to these questions. One speaker suggested that cell killing following internal exposures was potentially harmful in developing children.

In further discussion, a speaker welcomed Professor Wright's workshop review that had made clear the distinction between high and low LET effects, and which had discussed the notion of bystander saturation. These had been omitted in the Preliminary Report which seemed to be different from the presentations given by members. Another speaker stated on the other hand that epidemiological studies should capture all bystander and genomic instability effects. Others countered that, in the context of risk determination, current epidemiology studies may not pick up these effects due to their low statistical power.

A speaker questioned current ICRP estimates by drawing attention to work on the childhood leukaemia excesses near the Krümmel nuclear plant in Germany. Many examples of the dissonance between current risk factors and unexpected excesses existed in, for example, Germany, Belarus, Bavaria, and Ukraine. However, others questioned the veracity of these studies.

Various participants concluded it was important, for ethical and policy reasons, to involve the public in discussions about risk estimates. It was necessary for the Committee to help the public do this by providing a better feel for the size of the uncertainties surrounding current dose and risk models, as current ICRP estimates gave no indication of these uncertainties.

Professor Simmons and Dr Wakeford then presented alternative views on possible hormetic effects and the possibility of a dose threshold for cancer risk.

In discussion, a number of US speakers noted that hormetic/adaptive responses had not been seen in various US studies; other US speakers replied that hormetic effects were easily missed and quoted Raabe's work with dogs. On the other hand, various speakers noted that the A-bomb LSS data supported the linear no-threshold hypothesis, and that the ICRP and UNSCEAR continued to support the LNT model.

Other speakers stated that animal data showed low dose radiation stimulated antioxidant production; that ecological studies showed that in high background areas people seemed to live longer; and tissue culture data that demonstrated a reduction in spontaneous

carcinoma at low doses. However, others stated that there was an increase in Down's syndrome in Kerala, India, an area of high background radiation. In general, a clear division of views was expressed by participants on the shape of the dose–response curve at low doses which was noted by Committee members.

Tuesday 22 July 2003

Session 4 Epidemiological Studies: Part A

Dr Wakeford discussed cancer risks following *in utero* exposures. Dr Muirhead and Dr Busby set out alternative views on post-Chernobyl effects in Europe including UK.

In discussion, one speaker suggested that concerns about the risk of *in utero* tumour induction were overcautious, and the notion of enhanced risk in early pregnancy was difficult to tie down. Another speaker stated that, since it took a few years for leukaemia to develop, the suggested time frame for the peak in infant leukaemia post-Chernobyl seemed anomalous. A speaker suggested that the risk estimates Dr Busby derived from his epidemiological studies were too high. On the other hand, others stated that there could be serious problems with current post-Chernobyl risk analyses. With epidemiological evidence of both increased and decreased risks, a more precautionary approach should be deployed as regards current discharge authorisations.

Various Russian speakers questioned the emphasis on European, rather than Ukraine and Russian, study data. They were concerned with the results of studies on enhanced brain cancer after *in utero* irradiation, increased infant skin cancer in Belarus, and cancer of the sexual organs. Other speakers were concerned with the lack of interest in the severe health effects experienced in populations exposed from the Chernobyl accident. Despite problems associated with dose reconstruction, the radiological protection community should re-analyse the effects of the Chernobyl disaster. Some important potential health effects may have been overlooked.

Another speaker proposed comparing Chernobyl doses with background radiation, and calculating their collective doses: in this instance ICRP dose calculations were correct. However, others expressed concern with other post Chernobyl effects, including congenital malformations and early fetal development problems, seen in a number of countries. They questioned the accepted relationship between estimated doses and effects picked up in epidemiological studies. Others explained that a French–German initiative existed to support cancer, leukaemia, and congenital malformation registers in Belarus and Ukraine. A paper on increases in congenital malformations in Belarus and Ukraine had been submitted.

Russian speakers stated that 20–30 published papers existed concerning post-Chernobyl congenital malformations, including veterinary studies on cows. Many scientists were concerned with the reported high levels (50%) of mental retardation among newborn in exposed populations. It was suggested that the post-Chernobyl phenomena included a large increase in miscarriage and abortion rates resulting from heightened *in utero* susceptibility to radiation. However, others stated that the 1996 ECLIS preliminary report by IARC had reviewed this issue and found no increases in childhood leukaemia, although a more recent report was pending.

In further discussion on the results of epidemiological studies, speakers confirmed that infants and children who would have lived to develop leukaemia did sometimes succumb to earlier illnesses before presenting with leukaemia – and this could result in lower leukaemia registration rates. Other speakers suggested that leukaemia registrations had been suppressed in Belarus and other former Soviet republics.

Professor Darby and Dr Busby then presented alternative discussions on the effects from test bomb fallout.

A number of speakers stated that there was no cancer epidemic due to radiation pollution. Environmental damage from pollution was a small factor in cancer aetiology; the main causes were smoking, obesity, viral infections, and excessive alcohol consumption. However, others noted that much uncertainty existed on the effects of environmental chemical and radiation pollution on tissue formation and subsequent development. Studies in Chelyabinsk before and after the 1957 accident indicated a seven-fold increase in cancers due to pollution. Other speakers questioned the use of point-source models in estimating dose exposures, noting that it was better to employ more conservative specific activity models to assess doses. Later a speaker stated that Professor Darby's results were not compatible with ICRP risk coefficients: the Nordic data revealed risk estimated which were greater than ICRP estimates by a factor of around ten.

Session 5 Epidemiological Studies: Part B

Dr Busby and Dr Wakeford presented alternative discussions on UK ecological studies.

In discussion, a speaker noted that, as regards sea-to-land transfer, plutonium exposures would be only a small fraction of background radiation exposures, thus added risks would be small. On the other hand, it was said that a preliminary 1995 study in Dundalk, Ireland, indicated that the community was exposed to higher levels of high LET radiation. It was further suggested that an inflammatory effect could be associated with intakes of nanometre-sized particles that were expected to get through to the fetus. The pharmaceutical industry was already coating nanoparticles with drugs to increase uptakes via piggy-backing. It was noted that although mass was, at present, an important parameter for chemical regulatory purposes, toxicity was in fact a better guide.

On sea-to-land transfer, it was stated that the main questions were: (1) what size particles were we looking for, and (2) could they be detected? The answers to these questions were at present unknown, but it was suggested that there would be a problem if a 50 nm sized plutonium particle did get into the fetus. Such small particles could cause inflammation and cell proliferation, and could interact with radiation in the same way as other carcinogens did. In this connection, it was noted that injected sub-micron particles moved to lymph nodes and liver. The ICRP 1994 report contained calculations for very small particles down to 200 nm: the ICRP was continuing to consider this issue.

In further discussion, the population-mixing theory as proposed by Professor Kinlen was questioned in discussion. It was stated that a late challenge to a developing immune system in individuals in isolated populations might explain the increased disease incidence. However, this was questioned, as no infective agent had been isolated to explain the theory. A number of speakers further questioned the theory noting that the increased incidence of leukaemias near Sellafield was ongoing, and could not be explained by past population mixing in the 1950s and 1960s. The theory did not explain why the 8,000 newcomers who had built and worked the TNT plant at Windscale in the 1940s (before the construction of the nuclear facility) had also not caused an increase in disease due to population mixing. Other speakers reaffirmed their conviction that population mixing could explain the Seascale/Sellafield childhood leukaemia cluster. Others asked whether population-mixing and environmental radiation were mutually exclusive: multi-factorial and/or synergistic explanations existed for the acknowledged excesses. For example, medicines at normal doses could give quite unexpected responses when mixed with diets, eg blood pressure/anti-cancer drugs and grapefruit juice could produce fatal toxicity. It was stated that COMARE was reluctant to ascribe the excesses near Sellafield solely to population mixing: it was still examining the matter.

On Welsh ecological studies, a speaker noted that he had validated the new Welsh cancer register data, and had found that the main reason for the excess in the data supplied by the former Welsh cancer register was the misallocation of dates of birth. In further

discussion, other participants noted that the local health authority considered that the excess breast cancer incidence in Burnham near the Hinkley Point nuclear plant was due to increased screening for breast cancer.

Mr Bramhall then presented his views on the limitations of current epidemiology

In response, a number of speakers supported co-operation and joint fact-finding (ie agreement on the parameters of data acquisition, and the joint interpretation of results) which the Committee had explored. On access to data, a speaker stated that England and Wales cancer registries were not happy about current procedural restrictions on access to data, but they were legally hamstrung: even requests from the Committee would likely have to be cleared by an ethical committee. The situation was increasingly the same with cancer registries in Scotland, although they were not constrained by PIAG rules. It was stated that community access to health data was a valid challenge to the cancer registries.

Others stated that subtle changes at cellular level might be difficult to pick up via epidemiology with the result that (in the context of genomic instability) non-cancer effects might be attributed to radioactive pollution. Others worried whether there were changes in the background rate of common illnesses: the only way of determining this would be by increasing the resolution of epidemiological investigations and registrations.

Epidemiologists in the UK and other national cancer registries were concerned about increasing access constraints to data. Finland had laws governing the rights of the patient/community and registry obligations, but the release of health data concerning local clusters was reasonably quick – normally one or two months. Although support was expressed for the new numerator/denominator rule (which increased the numerator and, hence, allowed for less information to be accessed), it was suggested that the cancer registries should discuss this further with the ONS. However, others stated that the new numerator rule was itself a problem.

Wednesday 23 July

Session 6 Effects from Specific Sources of Internal Radiation

Dr Busby and Dr Cox discussed the second event hypothesis and its plausibility.

In discussion, a radiobiology speaker disagreed with the presented SET analyses. He stated that very high doses were needed to stimulate cell division from rest for cell replication, so it was doubtful that small doses would trigger a second event response. In addition, large doses were in fact involved in the induction of sarcomas. The assumption that background radiation was uniform was questioned, particularly the notion of averaging radon-daughter internal doses to tissues. Others noted that cell cycles, and hence cell sensitivity to radiation, were not uniform.

Dr Busby discussed natural and artificial sources of radioactivity and Professor Simmons discussed particulate sources.

In discussion, speakers referred to two studies where tumour yield from ‘hot’ particles was lower than that expected from uniform exposure. These were a Helsinki study where ^{90}Sr particles were injected under the skin, and a similar unpublished study on plutonium intakes at Bart’s Medical Hospital. This supported the view that ‘hot’ particles were not so risky.

It was concluded that a key problem was the lack of epidemiological information on internally exposed communities/populations. Existing published studies in Kerala suggested little difference between high and low background exposure regions: this might indicate there was no reason to distinguish between artificial and natural radiation. However, others replied that high background exposures in Kerala did have an effect on

the exposed community. Others noted that all exposures (including nuclear, industrial, background radiation and medical) could be viewed as being partly natural: the distinction between artificial and natural seemed quite arbitrary.

A speaker remained sceptical about Dr Busby's presentation stating that results from studies on Mayak workers had demonstrated a hormetic effect. Another speaker mistrusted the Mayak workers data because important results were concealed and remained unpublished. Petrushinka – a researcher in the same team – had discussed a study on 20,000 Mayak children in a small US/Russian symposium in 1999 and had concluded that their death rate was 100 times greater than predicted: 1 death per 200. Another speaker maintained that a distinction existed between man-made and background radiation with reference to new work by Kohnlein. However, other speakers disagreed with this view and pointed out that such a distinction made little scientific sense. Another speaker stated that a study in Ramsar, Iran, demonstrated a hormetic effect. In further discussion, another participant stated that when the Rongelap Islands' population had been asked to accept the dose of 1 mSv per year in the late 1980s, few had been willing to accept this.

Dr Fairlie and Dr Harrison then presented alternative discussions on the low energy emitter, tritium. Dr Harrison then set out his views on Auger emitters. The session concluded with the Chairman's discussion on alpha emitters.

In response to the discussion on tritium, a speaker noted that many factors were already incorporated into the current RBE for the isotope. He felt that some of these factors were double/triple counted in the Committee's Preliminary Report. After further discussion, he suggested that the enhanced prostate cancer associated with Winfrith reactor workers was not found in the other two reactor worker populations (Harwell and Dounreay), therefore this result could be anomalous. He also had queries about paucity of the tritium epidemiology cited in the circulated paper.

Session 7 Wider Considerations

A speaker presented a short discussion on post-Chernobyl health impacts. He concluded that there existed a wealth of Russian, Belarus, and Ukraine published studies that pointed to a stark increase in adverse health effects following the reactor accident. Others asked what impact genomic instability and the bystander effect had on cells, tissues and organs. They wondered how cancer/leukaemia epidemiology studies could help resolve the issue. A speaker proposed routine clinical analysis (such as the Bristol cohort study) in parallel with *in vitro* radiobiology work in order to address the issue of potential fitness loss.

Mr Bramhall then discussed ethical considerations in radiological protection. Dr Fairlie and Mr Dorfman discussed some reasons for polarised views on radiation risks.

Session 8 Future Work of CERRIE

Dr Fairlie presented the Committee's preliminary recommendations for future research and the Committee's next steps.

There followed a discussion on visitors' views on the Committee's future work.

A speaker presented a short discussion on the social implications of the internal radiation debate, in which he concluded that many of the issues were concerned with the interaction between science and ethical values. Others concluded that the concept of 'oppositional science' was a useful tool in the exploration of complex risk phenomena.

The Chairman thanked all the visitors for attending and all those who had contributed to making the meeting such a success.

The Workshop then ended.

CERRIE Workshop Participants

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Dr Hugo Baillie-Johnson	Norfolk and Norwich University Hospital
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Mr Roger Black	Scottish Cancer Intelligence Unit, Edinburgh
Mr Richard Bramhall	Low Level Radiation Campaign
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Dr Monty Charles	School of Physics and Astronomy, University of Birmingham
Mr Stuart Conney	Food Standards Agency
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Dr Roger Cox	National Radiological Protection Board
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Professor Timo Hakulinen	Finnish Cancer Registry
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