The Biological Basis of Radiation Protection – Standards for Low Doses of Ionising Radiation

John W. Stather, Chilton

Abstract

With developing knowledge of the effects of ionising radiation, interest has increasingly focussed on the effects of low doses and how information on dose response relationships for cancer can be used for setting limits on exposure for persons who are occupationally exposed and for members of the public. It is now believed that any radiation dose is capable of inducing cancer in exposed persons and that the probability of its occurrence, but not it's severity, depends on the radiation dose.

The main source of quantitative information on the risks of radiation-induced cancer comes from the long-term follow-up of the survivors of the atomic bombs in Hiroshima and Nagasaki. This database provides information on a population of more than 90,000 people followed up since 1950 with individuals of different ages exposed to whole body radiation. Information from this follow-up is supplemented by studies on persons exposed for medical reasons, either to external radiation or incorporated radionuclides, and people who have been exposed occupationally, in particular, miners exposed to radon and its decay products and luminisers exposed to radium.

In it's most recent recommendations, the International Commission on Radiological Protection, re-assessed the epidemiological data and this resulted in an increase in estimates of the risks of radiation-induced cancer. Partly this arose as a result of revised dosimetry for the A-bomb survivors and a longer follow-up of the population, but mainly it was attributed to a change in the model now used to project lifetime risks.

The development of the present risk coefficients for radiation-induced cancer both for the working population and for members of the public are described in this paper, with particular emphasis on the assessment of risks at low doses.

1. INTRODUCTION

The development of cancer is the major late effect resulting from exposure to radiation [2, 7, 38]. Cancer is generally understood to develop in a number of stages. That is, for malignancies to be expressed a series of events must occur in cells and the rate at which they occur is thought to be reflected in the way cancers appear in the population over the course of time.

Neoplasia in tissues is now seen as a complex, multi-stage process that can be subdivided into four phases: neoplastic initiation; promotion; conversion and progression. The sub-divisions are necessarily simplifications of the overall process which is, in any event, somewhat variable between different tumour types. However, they do provide a basis from which to interpret the cellular and molecular changes involved [37].

Neoplastic initiation encompasses the essentially irreversible cellular damage, which although not necessarily expressed immediately, provides the potential in cells for neoplastic development. There is good evidence that this initiation process results from damage to DNA leading to gene mutations in single target cells in tissues. The critical damage is likely to be coincident damage to both DNA strands (DNA double strand breaks). Although a proportion of such double strand damage will be

repaired, completely error free repair of such damage, even at low doses, is not expected. Neoplastic promotion can be seen as a process whereby initiated cells receive an abnormal growth stimulus and begin to proliferate in a semi-independent manner. Conversion of these pre-neoplastic cells to a form in which they are committed to become fully malignant is a central feature of the process of neoplastic development. Such changes are now believed to be driven by further gene mutations accumulating within the expanding population of pre-neoplastic cells.

Once the potential for full malignancy has been established, the subsequent progression of the disease may depend upon further cellular changes that allow invasion of adjacent normal tissues, the circulation of neoplastic cells in the blood and lymphatic systems and the establishment of metastases (secondary tumour growths) at other sites in the body. It is this invasive process that provides principally for the fatal effects of most common human tumours. On this basis, a single mutational event in a critical gene in a single target cell in vivo can create the potential for neoplastic development. Thus, a single radiation track traversing the nucleus of an appropriate target cell has a finite probability, albeit very low, of generating the specific damage to DNA that results in a tumour initiating mutation. These initiated cells can then develop by multistage processes into an overt malignancy. As a consequence, at the level of DNA damage, there is no basis for assuming that there is likely to be a dose threshold below which the risk of tumour induction would be zero. For radiation protection purposes, a progressive increase in risk with increasing dose, with no threshold, is therefore assumed [5].

Radiation is capable of causing tumours in nearly all tissues of the body, although the frequency of appearance following a unit dose may vary markedly from one tissue to another. Information on the dose related frequency of tumour induction by radiation is gained through follow up of groups of persons exposed to radiation. The observed tumour frequency can then be compared with an age and sex matched control group, not exposed to radiation, to determine the increase in frequency due to radiation exposure.

Tumours induced by radiation are in general indistinguishable from those occurring spontaneously and since cancer is not uncommon (about one in five die as a result of it), the problem of determining a relatively small excess due to radiation is difficult. In general large exposed populations are necessary to obtain statistically meaningful results.

The chief sources of information on the risks of radiation induced cancer are the A bomb survivors exposed to whole body irradiation in Hiroshima and Nagasaki, patients with ankylosing spondylitis and other patients who were exposed to partial body irradiation therapeutically, either from external radiation or internally incorporated radionuclides, and various occupationally exposed populations, such as uranium miners and radium dial painters.

2. DOSE RESPONSE RELATIONSHIPS

There is always a minimum period of time between irradiation and the appearance of a radiation induced tumour. This period is termed the latent period and its length varies with age and from one tumour to another. Some types of leukaemia and bone cancer have latent periods of only a few years but many solid tumours have latent periods of ten or more years. For leukaemia and bone cancer there is fairly good evidence that the risk is completely expressed within about twenty-five years following exposure. For tumours of longer latency, such as those of the GI tract and liver, it is not yet clear whether the incidence

of these tumours passes through a maximum and declines with time following exposure or whether the risk levels out or alternatively increases indefinitely during the remainder of life.

To project the overall cancer risk for an exposed population, it is therefore necessary to use models that extrapolate over time data based on only a limited period of the lives of the individuals. Two such projection models have generally been used:

(a) the additive (absolute) risk model which postulates that radiation will induce cancer independently of the spontaneous rate after a period of latency, variations in risk may occur due to sex and age at exposure

(b) the multiplicative (relative) risk model in which the excess (after latency) is given by a constant factor applied to the age dependent incidence of natural cancers in the population.

In most cases this spontaneous risk increases with age and therefore the multiplicative model will predict an increasing incidence of cancer with increasing age. The relative risk model also gives different risks of radiation-induced cancer in different populations, depending on the national cancer incidence. Data available from the A bomb survivors in Japan and from studies on uranium miners suggest the multiplicative projection model gives a better fit to the data, at least for some of the most common cancer types (Table 1). Despite this there are indications from a number of exposed groups that the risk of cancer may start to decline many years after exposure. This has been well documented for leukaemia, but has also been observed in the case of bone cancers (German ^{224}Ra cases), thyroid cancers (US follow up study after thymus irradiation), solid cancers (ankylosing spondylitics) and possibly lung cancers in the uranium miners. These results suggest that for the Japanese population the excess risk may ultimately decrease with time and thus multiplicative projection models applied over a lifetime could result in an overestimate of the cancer risk.

Dose and dose rate both influence cancer induction and are linked to the form of the dose response relationship. For radiological protection purposes tumour induction is generally assumed to increase with increasing dose, with no threshold, as indicated above. However, studies from cells in culture reveal that for many endpoints, including mutation, the dose response is not linear, but that the effectiveness of radiation, per unit dose, increases as the dose increases. At very low doses, where there is a low probability of more than one radiation event occurring in a cell nucleus it may be expected that the effect is linearly related to dose. At higher doses, where multiple ionising events within a single cell are commonplace, damage arising from interactions between two or more events becomes probable.

The difficulty in assessing risks of cancer following exposures to low LET radiation at low doses and dose rates is illustrated in the Figure. This gives, schematically, data points and possible dose response curves for cancer induction. Frequently, as in this example, information is only available at relatively high doses. An approach commonly used in risk assessment is to fit a linear dose response relationship to the data (curve B) a procedure usually considered to give an upper limit to the risk at low doses. This will be the case unless significant cell killing has occurred. If this linear relationship is due to single tracks acting independently then the effect per unit dose would be expected to be independent of dose magnitude and dose rate. In practice, however, this is not generally observed and the linear quadratic relationship (curve A) frequently gives a better fit to the data at low to intermediate doses implying that at higher doses damage is the result of both single and multiple tracks. At still higher

doses cell killing becomes significant with a consequent reduction in tumour yield.
With a progressive lowering of the dose and the dose rate, allowing more opportunity for repair of damage, a point may ultimately be reached at which multiple track events make a negligible contribution to tumour incidence and damage is produced only as a result of single tracks acting alone giving a linear response (curve D) with the effect proportional to dose (slope 1, the risk coefficient). A similar response would be obtained by lowering the dose rate alone as even with high total doses the rate of build up of lesions would be slower and the opportunity for multiple track events would decrease. Hence in the limit, curve D, could be achieved either by reducing the dose to very low values so that effects are independent of dose rate or by reducing the dose rate to very low values. The approach used for assessing risks at low doses and low dose rates of low LET radiation is described in Sections 5 and 6. For high LET radiation it is assumed that there is no dose rate effect and the response is proportional to dose for doses below those at which there is cell killing.
The data on the A-bomb survivors provide information on risks of cancer in a range of tissues, although to date no information is available under the new dosimetry for radiation-induced cancers of the liver, cells on bone surfaces, thyroid and skin. Information on radiation induced cancer in these tissues is, however, available from other epidemiological studies summarised in Table 2. The principal studies used to quantify the effects of both external radiation and internally incorporated radionuclides are summarised below.

3. EXPOSURES TO EXTERNAL RADIATION

3.1 The A-bomb Survivors in Japan

The mortality experience of the Hiroshima and Nagasaki A bomb survivors has been the single most important source of information on the risk of radiation-induced cancer. Information is available on the exposure of individuals to whole body radiation at a range of ages. New data that became available in the 1980s on this population of more than 90,000 people in the Life Span Study (LSS) followed up since 1950 necessitated a revision of previous risk estimates [23, 26]. There were a number of components to this change. The first is a revision of the dosimetry (DS86) to allow, amongst other factors, for the high humidity in the air over the cities which has substantially reduced the neutron dose at Hiroshima from the earlier 1965 (T65) estimates which were based on measurements in the dry atmosphere of the Nevada desert. Improved estimates have also been made of the yield of the Hiroshima bomb (increased from 12.5 to 15 ktonnes), the shielding provided by buildings and of tissue and organ doses. The second is that the number of excess fatal cancers in the population has increased due to the increased period of follow up (to 1985) and an estimate of the cancers occurring in the period 1945-1950 have now been made. The third is that multiplicative, rather than additive risk models appear to provide a better basis for assessing lifetime risk of most solid cancers.
UNSCEAR (1988) in a report to the General Assembly provided information on radiation induced cancer risks for a number of tissues in the Japanese population based on both additive and multiplicative projection models. The total cancer risk at high dose and high dose rate was estimated to be

4 and 7 10^{-2} Sv^{-1}* using the additive and multiplicative models respectively and an age averaged risk coefficient. This compared with the Committee's 1977 assessment of 2.5 10^{-2} Sv^{-1} at high dose rate using the additive model [33]. Because children and young persons are more sensitive to radiation than adults the application of age specific risk coefficients increases the predicted numbers of radiation induced cancers.

These risk estimates for whole body radiation exposure were based on an extrapolation into the future which is somewhat uncertain for solid cancers because two thirds of the Japanese survivors are still alive and two thirds of the cancer risk has still to be expressed. Up to 1985 about 80 excess leukaemias and 260 excess solid cancers had occurred in the LSS population for whom DS86 doses are available out of a total of about 6000 cancer deaths [23]. The risk of radiation-induced leukaemia is more certain than that for solid cancers, however, as few more excess cases are now expected. There are also uncertainties in extrapolating the cancer risks based on the Japanese population exposed to radiation at high dose rates to the low doses and dose rates relevant for radiological protection purposes (see Section 5). Further data on mortality in the A-bomb survivors are expected to be published during 1996.

3.2 Thyroid Cancer

Groups of children and young persons who received thyroid irradiation, and who can be used to derive risk coefficients for thyroid cancer, include children who received X ray treatment for thymic enlargement, patients treated in US hospitals for thyrotoxicosis and other benign lesions of the neck and patients who received X ray treatment for thyroid disease [21, 27]. In the majority of cases, particularly in the young, thyroid cancer is not fatal. The mortality from radiation-induced thyroid cancer is expected to be about 10% of the incidence. There is also evidence that the risk in adults is about half that in children and that the risk in females is about twice that in males. For a population uniformly exposed to external radiation the risk of fatal thyroid cancer is estimated to be 8.0 10^{-4} Gy^{-1} assuming a 5 year latent period [8]. In human populations given iodine 131 for non therapeutic reasons, and who received doses well below 2 Gy, no significant excess of thyroid cancers has been observed. This suggests a risk coefficient 3 to 4 times less than that obtained following external radiation at high dose rates [21]. Data on thyroid cancer incidence in children in areas of the former Soviet Union that were contaminated with fall-out from Chernobyl indicate an increased risk of thyroid cancer in some areas. To date the data are insufficient to provide quantitative risk estimates.

3.3 Skin Cancer

An ICRP Task Group [9] has reviewed data on the risks of skin cancer. Most of the data come from groups given partial body irradiation in the course of medical treatment, although some data are available from occupationally exposed groups, in particular radiologists and radiation technicians and uranium mining populations. Little information is available from the A-bomb survivors. On the basis of a relative risk model, the Task Group calculated a risk of fatal skin cancer for exposure of a general population of 2 10^{-4} Sv^{-1} at low doses, on the assumption that 0.2% of cases would be fatal. The Task Group stressed the uncertainty over assessing the temporal pattern of radiation-induced skin cancers.

* A risk of 1 10^{-2} Sv^{-1} corresponds to a risk of cancer of 1 in 100 per Sv or 1 in 100,000 per mSv.

3.4 Breast Cancer

Data are available on radiation-induced breast cancer from follow-up studies on the A-bomb survivors as well as from studies of patients in North America given fluoroscopy examinations for tuberculosis or treated for acute postpartum mastitis [15]. Risks calculated from either population are little different, based on additive projection models. ICRP has based its risk estimate of $2\ 10^{-3}\ Sv^{-1}$, for a mixed population of men and women, on the data on the A-bomb survivors [8]. The risk of breast cancer also varies considerably with age at exposure. Thus, for exposure in the first decade of life, the risk is about 4 times that at ages 40-50 years [19].

4. EXPOSURE TO INTERNALLY INCORPORATED RADIONUCLIDES

Human data on the effects of internally incorporated radionuclides are available for only a few radionuclides and have been reviewed by UNSCEAR (1994). Quantitative data for risk estimation are available only for alpha particle emitters.

The available information covers groups exposed to radium isotopes (^{224}Ra, ^{226}Ra, ^{228}Ra) where bone tumours are the predominant late effect, and Thorotrast (colloidal ThO_2) which principally results in irradiation of the liver, spleen and bone marrow, with tumours arising mainly in the liver and bone marrow (leukaemia). Information is also available in man on lung cancer following exposure to radon and its decay products. Epidemiological studies of domestic exposure to radon are presently under way, but it will be some time before sufficient data are available to obtain an indication of possible risks. Twenty-six men who worked with plutonium on the Manhattan project during the Second World War have also been studied (estimated body contents 52-3180 Bq). Seven individuals have so far died. The causes of death were lung cancer (2 cases), myocardial infarction, arteriosclerotic heart disease, accidental injury, respiratory failure due to pneumonia/congestive heart failure and osteosarcoma of the sacrum. Three men also reported a history of skin cancer. There is a high probability that the bone cancer was caused by exposure to plutonium as the spontaneous risk is about 1 in 2000.

4.1 Radium-226/228 Luminisers

An increased incidence of bone cancer and of head sinus carcinoma has been observed in persons exposed to long lived radium, particularly in painters of luminous dials, but also radium chemists or persons treated with radium salts for a possible therapeutic effect [24, 25]. These persons became internally contaminated with pure ^{226}Ra ($t½$ = 1,600 years) in some cases, and in other cases with various mixtures of ^{226}Ra and ^{228}Ra ($t½$ = 5.77 years). Bone cancers and head sinus carcinomas have arisen in these populations. The majority of these cancers had appeared by 1969, although three bone tumours have appeared since then and head cancers have recently appeared at a greater rate than bone cancers. The radium isotopes deposit principally in the skeleton and the bone sarcomas appear to have been induced by particles from either the ^{226}Ra or ^{228}Ra decay series. The head sinus carcinomas are thought to be caused mainly by the accumulation of radon (^{222}Rn) gas in the frontal sinuses and mastoid air cells. This radon is produced by the decay of ^{226}Ra in the bone.

Except for the bone sarcomas and head sinus carcinomas no definite excess in other types of malignancy, including leukaemia, is presently ascribed to the internal deposition of long lived radium.

4.2 Radium-224 Patients

The effects of intakes of radium has also been studied in German patients injected with ^{224}Ra shortly after World War II. The study group consists of a population of 682 adults and 218 juveniles (age at first injection varied between 1 and 20 years) who received weekly or twice weekly intravenous injections of ^{224}Ra, mainly for the treatment of bone tuberculosis or ankylosing spondylitis [14, 29]. The last bone tumour occurred in 1988, 41 years after the injection of ^{224}Ra into a three year old boy and is the only bone sarcoma reported in this series since 1974. Very few new tumours are now expected.

Based on the information on bone cancer risks following intakes of radium, ICRP (1991a) has adopted a total risk estimate of $5\ 10^{-4}\ Sv^{-1}$ (assuming a radiation weighting factor for -particle irradiation of 20).

4.3 Miners Exposed to Radon

An increased mortality from lung disease has been observed in under-ground miners working in Czechoslovakia, Canada, United States of America and Sweden exposed to ^{222}Rn and its decay products [1].

The increase in mortality from lung cancer has been correlated with air concentrations of radon in different mines and the duration of exposure. Bronchial stem cells and secretion cells in the airways are considered to be the main target cell for the induction of lung cancer resulting from radon exposure. There are many difficulties in calculating the radiation dose to these cells as a result of exposure to radon decay products (expressed in working level months**). The radiation dose over the working life must be taken into account and the dust loading of the atmosphere known as it determines the extent of absorption of radon daughters onto the respirable particles. In addition to any possible synergistic effects between smoking and radon exposure, the presence of dust, diesel fumes and other possible carcinogens in the mine atmosphere causes some uncertainty as to whether an excess of cancer can be attributed to radiation alone. The BEIR IV Committee have suggested a risk of lung cancer following exposure to radon and its decay products of 350 cases per 106 persons per WLM. This corresponds broadly to a risk of $0.42\ 10^{-2}\ Sv^{-1}$ following exposure of the lung ($3.5\ 10^{-2}\ Sv^{-1}$, Effective Dose), assuming a radiation weighting factor, w_R for irradiation of 20 and is similar to the value of $0.68\ 10^{-2}\ Sv^{-1}$ adopted by ICRP [7] for a working population based on the A bomb survivors.

4.4 Thorotrast Patients

Thorotrast is colloidal thorium oxide. In the late 1920s it began to be injected into the arteries of patients for use in diagnostic radiology as an X ray contrast material. The average dose of about 25 ml of Thorotrast contained 5 gms of thorium with an activity ( ) of about 20 kBq ^{232}Th with additional radioactivity from its decay products. The colloidal Thorotrast was cleared from the bloodstream by uptake into phagocytic cells depositing about 60% in liver, 30% in spleen and 10% in red marrow. Extensive epidemiological studies in Portugal, Sweden, Denmark, the United States, the Federal Republic of Germany and Japan have shown that retention of thorium oxide particles in the liver and in the bone marrow has resulted in an increased risk of liver tumours and leukaemias as well as liver cirrhosis and other cardiovascular diseases [1, 39, 40]. On the basis of an injected dose of 25 ml the dose to the liver is estimated to be $0.25\ Gy\ y^{-1}$. Present estimates, based on

** 1 WL is any combination of the short-lived decay products of radon per litre of air which will result in the ultimate emission of 1.3×10^5 MeV of particle energy. A WLM results from exposure to a concentration of decay products in air of 1 WL for an average working month of 170 hours at a breathing rate of $1.2\ m^3\ h^{-1}$.

a latent period of 20 years, suggest a lifetime risk of liver cancer following exposure to Thorotrast of about 0.15 10^{-2} Sv^{-1} [1, 7], about half this risk is expected to be expressed by 40 years after exposure.

5. DOSE AND DOSE RATE EFFECTIVENESS FACTORS (DDREFs)

Risk coefficients for radiation induced cancer are mainly based on population groups exposed at high doses and high dose rates. Studies at the molecular, cellular, tissue and whole animal level have demonstrated that radiation damage increases with dose and that, at least for low LET radiation, at high dose rates it is often greater per unit of exposure than at low dose rates. Thus, although the assumption normally made for radiation protection purposes is that the dose response curve for cancer induction is linear, with the risk proportional to dose, in practice a dose and dose rate effectiveness factor (DDREF) has commonly been used to allow for a reduced effectiveness of radiation in inducing cancer in man at low doses and low dose rates. The choice of a suitable DDREF has caused considerable debate with relevant data being available from cellular and animal studies, as well as human epidemiology.

In 1986 UNSCEAR suggested that for many cancers the assumption of a linear response when extrapolating from information at high dose rates could overestimate risk at low dose rates by up to a factor of 5 [35]. In 1988, UNSCEAR stated that risks at low dose rates of low LET radiation may be less than high dose rates by a factor of between 2 and 10 [36]. Similar conclusions were reached by the BEIR V Committee. UNSCEAR in its 1993 report comprehensively reviewed experimental and epidemiological data relevant to the choice of DDREF. The Committee suggested an appropriate value of DDREF was < 3. ICRP in its 1990 recommendations based estimates of DDREF principally on an analysis by Pierce and Vaeth (1989) of the data from the Japanese survivors. This analysis shows that the data do not allow for a reduction factor of much more than about 2. Other epidemiological data showed little evidence of dose rate effects although studies on thyroid cancer incidence [28] and breast cancer mortality [15] indicate possible reduction factors of up to 3 or 4. As a consequence ICRP [8] have adopted a DDREF of 2, recognising that "the choice is somewhat arbitrary and may be conservative". In practice, the DDREF would be expected to vary with tissue and exposure conditions although a single value has had to be assigned for protection purposes. A better understanding of the mechanisms involved will be essential for improving understanding of the effects of both dose and dose rates on radiation-induced tumour induction in man. A summary of values of DDREF recommended by national and international bodies is given in Table 3. No DDREF is recommended for high LET radiation.

6. RISK COEFFICIENTS FOR RADIATION-INDUCED CANCER

In the last few years a number of studies have been published which have calculated risks of radiation induced cancer for different populations. They have been based predominantly on information derived from the A-bomb survivors but supplemented by data from other epidemiological studies. Most risks have been calculated for the general population, although a number of reports have also given risks for workers. These tend to be lower (by about 20 40%) because of the greater risk to children and young persons calculated using the relative risk projection model for most solid cancers.

Table 4 summarises the information on somatic radiation risks at high doses and high

dose rates published in recent years by UNSCEAR (1988), BEIR (1990), NRPB (Muirhead et al , 1993) and ICRP (1991a), using mainly relative risk projection models for most solid cancers. In the majority of studies lifetime risks of cancer have been calculated, although NRPB also gave risks to 40 years after exposure (the present period of follow-up of the A-bomb survivors). UNSCEAR (1988) calculated risks based on both an age-averaged and an age-specific constant relative risk models. BEIR V (1990) calculated risks to a US population and gave values for a number of tissues using time-varying relative risk models for some cancers (leukaemia, respiratory tract, breast cancer in females). It is noteworthy that BEIR V, unlike UNSCEAR, calculated excess cancer deaths, not early deaths. The former risk is about 20-25% less than the latter reflecting the baseline cancer rate in the population. ICRP (1991a) calculated risks for a 'world' population based on an average value for five populations (Japan, UK, USA, Puerto Rico, China) and on transferring both absolute and relative risks across populations.

Overall the lifetime risks calculated in recent years are not too different for the various studies, the lowest value being for UNSCEAR (1988) using age-averaged risk coefficients. ICRP (1991a) have adopted a rounded value of 10 10^{-2} Sv^{-1} for the risk coefficient for fatal cancer at high doses and high dose rate following exposure of a mixed population of all ages. Applying a DDREF of 2 gives a risk of 5 10^{-2} Sv^{-1} for radiation protection purposes. Risk coefficients for individual tissues are given in Table 5, which also gives risk coefficients recommended by ICRP in 1977. For workers the risk coefficient adopted for radiation protection purposes is 4 10^{-2} Sv^{-1}.

7. LOW DOSE STUDIES

The majority of studies on which risk estimates for radiation-induced cancer are based are for populations exposed at high doses and high dose rates. Studies of low dose rate exposure generally involve low doses and because of the likely low excess risks are hampered by lack of statistical power and possibly also by confounding factors. However low dose rate studies can provide a check on the risks derived by extrapolation from high dose rate studies. The main studies of interest are on workers who are occupationally exposed although some data are also available on risks in children following exposures *in utero* and on persons from areas of high natural background.

7.1 Occupational Exposures

Several studies have been conducted of nuclear industry workers. In the USA, Gilbert et al, (1989) performed a joint analysis of data for about 36,000 workers at the Hanford site, Oak Ridge National Laboratory and Rocky Flats weapons plant. Neither for the grouping of all cancers nor for leukaemia was there an indication of an increasing trend in risk with dose.A study of just over 95,000 individuals on the UK's National Registry for radiation Workers (NRRW) has examined cancer mortality in relation to dose [10]. For all malignant neoplasms, the trend in the relative risk with dose was positive but was not statistically significant (p=0.10). Based on a relative risk projection model, the central estimate of the lifetime risk based on these data was 10% Sv^{-1}, which is 2½ times the value of 4% Sv^{-1} cited by ICRP (1991a) for risks associated with exposure of workers (based on applying DDREF of 2 to the Japanese data). The 90% confidence interval for the NRRW-derived risk ranged from a negative value up to about 6 times the ICRP value. For leukaemia (excluding chronic lymphatic leukaemia (CLL) which does not appear to be radiation inducible), the trend in risk with dose was statistically significant (p=0.03). Based on a BEIR V - type pro-

jection model (BEIR, 1990), the central estimate of the corresponding lifetime leukaemia risk was 0.76% Sv^{-1} which is 1.9 times the ICRP value for a worker population (0.4% Sv^{-1}), with 90% confidence limits ranging from just above zero up to about 6 times the ICRP value. There were also an indication of an increasing trend with dose in the risk of multiple myeloma (p=0.06), the estimated trend in the relative risk was about 3 times that obtained from the Japanese survivor data under a linear dose-response model, with a 90% confidence ranging from just under zero up to 20 times the Japanese value. An increasing trend in multiple myeloma risk with dose was similarly found in the US study of Gilbert et al (1989) ($p < 0.05$).

The National Registry for Radiation Workers therefore provides evidence of raised risks of leukaemia and multiple myeloma associated with occupational exposure to radiation, but, like the combined study of US workers [6], is consistent with the risk estimates for low dose/dose rate exposures derived by ICRP (1991a) from the Japanese survivor data. In particular, combining the NRRW and US results produces central estimates for lifetime risk of 4.9 10^{-2} Sv^{-1} (90% CI <0, 18) for all cancers and 0.30 10-2 Sv-1 (90% CI <0, 1.04) for leukaemia, excluding CLL (Kendall et al, 1992b), which are similar to the ICRP risk estimates.

7.2 Exposures *In Utero*

A number of studies have been published that have examined the risks of cancer in childhood following exposures *in utero*. These studies have particular advantages for detecting risks of cancer at low doses because of the low spontaneous cancer rate in children.

The Oxford Survey of Childhood Cancers (OSCC) is a case-control study and was started in the mid-1950s. Up to 1979, mothers of 14,759 cases and the same number of matched controls had been interviewed. During the late 1950s, the study investigators reported a doubling in the risk of childhood cancer associated with prenatal x-ray exposure. Later analysis covering a longer period indicated a falling risk with time and average raised risk of about 40% (95% CI: 31-50) [3, 30, 31]. Although there is some uncertainty in the doses received, they are considered to fall in the range for about 5 to 20 mGy (low-LET) [33].

It has been suggested that, owing to the retrospective nature of the OSCC, with at least partial reliance upon mothers' memories, some bias may have been introduced. The results of the follow-up were supported by a study in the United States based on contemporary records of x-ray exposure; an association between prenatal x-rays and childhood cancer was confirmed [13, 17].

The possibility still exists that there may be some, as yet unidentified, confounding factor in the OSCC affecting both the probability of the fetus being irradiated *in utero* and the risk of subsequent cancer. The data obtained in the survey were reanalysed, however, by Mole (1974), who showed that the frequency of leukaemia and of solid cancers in childhood is greater following prenatal x-radiography, not only in singleton births, but also in dizygotic twins. The radiography rate was 10% in singletons and 55% in twins. A similar excess frequency of leukaemia and of solid cancers in those x-rayed with such different rates of radiography provides evidence for irradiation as the cause.

The effect of other possible confounding factors such as sibship position, maternal age and social class was considered by Bithell and Stewart (1975) and by Kneale and Stewart (1976). Generally, the relative risk associated with prenatal x-rays was changed little after allowing for these factors [18].

Other case-control studies give estimates of the relative cancer risk associated with ex-

posure to x-rays *in utero* that are greater than 1.0. Bithell (1989) has shown that the relative risks obtained from 13 additional studies are consistent with information from the OSCC, even though they relate to different populations and the studies sometimes differ in their design and method of analysis. With the OSCC excluded, the weighted average of the relative risks is 1.36 (95% CI: 1.20-1.51), which is significantly greater than unity and is consistent with the estimate of 1.4 obtained from the OSCC. Inclusion of the OSCC estimate yields an average relative risk of 1.39 (98% CI: 1.31-1.47).

While no excess of childhood cancer has been observed among those exposed to atomic bomb radiation *in utero*, there is only borderline evidence that this result differs to a statistically significant extent from the OSCC [42]. Among 1263 children irradiated *in utero* and followed from birth, 2 cases of cancer arose up to 15 years of age, compared with 0.73 expected from Japanese national rates [41]. The resulting upper limit on the 95% CI for the absolute radiation-induced risk is 2.8 10^{-2} Gy^{-1} (low-LET). Continued follow-up showed an excess of adult cancers among those exposed to atomic bomb radiation *in utero*. Based on the follow-up to 1984, the relative risk at 1 Gy was estimated to be 3.77, which is similar to that seen among survivors of the atomic bombings irradiated in the first 10 years of life [26]. Further follow-up to the end of 1989 suggested a subsequent decrease in the relative risk [42], in line with the pattern indicated by the earlier follow-up of those exposed postnatally at ages under 10 years.

Thus, although there is some consistency in the case-control studies in showing a raised risk of childhood cancer, the absence of confirmation in cohort studies leaves some uncertainty in establishing a risk estimate. Muirhead et al (1993) have estimated a risk of cancer incidence of 6 10^{-2} Sv^{-1} to age 15 years following irradiation *in utero* from the OSCC data. Since slightly less than 50% of childhood cancers consist of leukaemia and other lymphatic/haemopoietic cancers, and the relative risks are similar for these and other cancers, a risk of 2.5 10^{-2} Gy^{-1} may be assumed for leukaemia and 3.5 10^{-2} Gy^{-1} for solid cancers. Also, as slightly less than half of all childhood cancers are fatal, the number of excess cancer deaths may be taken as 3 10^{-2} Gy^{-1}, comprising 1.25 10^{-2} Gy^{-1} for leukaemias and 1.75 10^{-2} Gy^{-1} for solid cancers. As seen in the OSCC, all increase in childhood cancer risk may arise from doses in the range of about 5-20 mGy (low-LET).

7.3 Background Radiation

Studies of exposure to natural radiation (other than radon) have generally involved looking for any geographical correlation with cancer rates. Such studies are difficult to interpret however owing to the effect of confounding factors such as socio-demographic variables and other factors that vary geographically.

8. SUMMARY OF RISK FACTORS FOR THE GENERAL POPULATION AND WORKERS USED IN SETTING DOSE LIMITS

The International Commission on Radiological Protection [8] now considers four components of the detriment (health effects) due to irradiation of the tissues and organs of the body at low doses when assessing the overall effects of radiation. These include the probability of fatal cancer; the probability of non-fatal cancer and the probability of severe hereditary disease, both weighted for severity relative to fatal cancer; and the time scale of appearance of these detrimental effects. The overall weighted severity values assigned to the non-fatal cancers and severe hereditary diseases (including multifactorial diseases)

each amount to about one-fifth of the detriment associated with fatal cancer. In summary the aggregated detriment amounts to 7.3×10^{-2} Sv^{-1} for a nominal population. It is slightly less (5.6×10^{-2} Sv^{-1}) for a population aged 18-64 years who are occupationally exposed, when account is taken of the omission of younger persons who are more radio-sensitive and the shorter mean potential period of reproduction. The risk factors recommended by ICRP for protection purposes are summarised in Table 6.

9. FUTURE PROSPECTS

There remain a number of important questions that remain to be answered in the assessment of the risks of radiation-induced in human populations. Very limited information is available at the low doses and low dose rates that are important for radiation protection and the risks have to be assessed principally from populations exposed at high doses and dose rates by applying an appropriate dose and dose rate effectiveness factor. Increasingly, however, epidemiological studies on groups of workers in the nuclear industry are providing information on exposures at low doses and dose rates although at present any estimates of risk have large uncertainties associated with them. With the development of these national studies and by pooling them internationally by the International Agency for Research in Cancer, these uncertainties should be progressively reduced. The projection of lifetime risk remains uncertain, particularly for those exposed at younger age groups, and is largely based on empirical fits to the epidemiological data obtained to date. Continued follow up of exposed populations, in particular the A-bomb survivors in Japan is needed for validating current models. It seems likely that epidemiological studies will be unable to answer all the questions concerned with the effects of dose, dose rate, radiation quality and individual sensitivity on cancer induction. Ultimately this must depend on a much better understanding of the response of tissues to radiation. This will come partly from carefully controlled animal studies but increasingly from cellular and molecular studies on the fundamental mechanisms involved in cancer induction.

REFERENCES

1 BEIR IV. Health Risks of Radon and Other Internally Deposited Alpha emitters. National Academy Press. Washington DC (1988).

2 BEIR V. Health Effects of Exposure to Low Levels of Ionizing Radiation. National Academy Press. Washington DC (1990).

3 Bithell, J F, and Stewart, A M. Pre natal irradiation and childhood malignancy: A review of British data from the Oxford Survey. Br. J. Cancer, 35: 271-287 (1975).

4 Bithell, J F. Epidemiological studies of children irradiated *in utero*. p.77-87 in: Low Dose Radiation: Biological Bases of Risk Assessment (K F Baverstock and J W Stather, eds.). Taylor and Francis, London (1989).

5 Cox, R, Muirhead, C R, Stather, J W, Edwards, A A, and Little, M P. Risk of Radiation-induced Cancer at Low Doses and Low Dose Rates for Radiation Protection Purposes. Docs. NRPB 6(1) (1995).

6 Gilbert, E S, Fry, S A, Wiggs, L D, Voelz, G L, Cragle, D L, and Petersen, G R. Analyses of combined mortality data on workers at the Hanford site, Oak Ridge National Laboratory and Rocky Flats nuclear weapons plant. Radiat. Res., 120: 19-35 (1989).

7 International Commission on Radiological Protection. Recommendations of the International Commission on Radiological Protection. ICRP Publication 26. Oxford, Pergamon Press (1977).

8 International Commission on Radiological Protection. 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Annals of the ICRP 21(1 3). Oxford, Pergamon Press (1991a).

9 International Commission on Radiological Protection. The Biological Basis for Dose Limitation in the Skin. ICRP Publication 59. An-

nals of the ICRP, 22(2). Oxford, Pergamon Press (1991b).

10 Kendall, G M, Muirhead, C R, MacGibbon, B H, O'Hagan, J A, Conquest, A J, Goodill, A A, Butland, B K, Fell, T P, Jackson, D A, Webb, M A, Haylock, R G E, Thomas, J M, and Silk, T J. Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. Br. Med. J., 304: 220-225 (1992a)

11 Kendall, G M, Muirhead, C R, MacGibbon, B H, O'Hagan, J A, Conquest, A J, Goodill, A A, Butland, B K, Fell, T P, Jackson, D A, Webb, M A, Haylock, R G E, Thomas, J M, and Silk, T J. First analysis of the National Registry for Radiation Workers: occupational exposure to ionising radiation and mortality. Chilton, NRPB R251 (London, HMSO) (1992b).

12 Kneale, G W, and Stewart, A M. Mantel-Haenszel analysis of Oxford data. I. Independent effects of several birth factors including fetal irradiation. J. Natl. Cancer Inst. 56: 879-883 (1976).

13 MacMahon, B. Prenatal x-ray exposure and childhood cancer. J. Natl. Cancer Inst. 28: 1173-1191 (1962).

14 Mays, C W, Spiess, H, Chemelevsky, D, and Kellerer, A. IN Proc. Symp. "The Radiobiology of Radium and Thorotrast". Eds. W. Gössner, G.B. Gerber, J. Hagen, A. Luz. Neuherberg 29-31 Oct, 1984. Strahlentherapie 80 Suppl. 14-21, pp 27-31 (1986).

15 Miller, A B, Howe, G R, Sherman, G J, Lindsay, J P, Yaffe, M J, Dinner, P J, Risch, H A, and Preston, D L. Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated from tuberculosis. N. Eng. J. Med. 321, 1285-1289 (1989)

16 Mole, R H. Antenatal irradiation and childhood cancer. Causation or coincidence? Br. J. Cancer 30: 199-208 (1974).

17 Monson, R R, and MacMahon, B. Prenatal x-ray exposure and cancer in children. p.97-105 in: Radiation Carcinogenesis: Epidemiology and Biological Significance (J D Boice and J F Fraumeni, eds.). Raven Press, New York (1984).

18 Muirhead, C R, and Kneale, G W. Prenatal irradiation and childhood cancer. J. Radiol. Prot. 9: 209-212 (1989).

19 Muirhead, C R, Cox, R, Stather, J W, MacGibbon, B H, Edwards, A A, and Haylock, R G E. Estimates of late radiation risks to the UK population. Docs. of NRPB, 4 (4) (1993).

20 National Council on Radiation Protection and Measurements. Influence of dose and its distribution in time on dose response relationships for low LET radiation. Washington DC, NCRP Report No. 64 (1980).

21 National Council on Radiation Protection and Measurements. Induction of thyroid cancer by ionising radiation. NCRP, Report No. 80. (1985).

22 Pierce, D A, and Vaeth, M. Cancer risk estimation from the A-bomb survivors: Extrapolation to low doses, use of relative risk models and other uncertainties. In Low Dose Radiation Biological Bases of Risk Assessment, (Eds K F Baverstock and J W Stather). Taylor and Francis, London, pp 54-75 (1989).

23 Preston, D L, and Pierce, D A. The effects of changes in dosimetry on cancer mortality risk. Estimates in the atomic bomb survivors. Hiroshima, Radiation Effects Research Foundation, RERF TR 0 87 (1987).

24 Rowland, R E. Radium in Humans. A Review of US Studies. ANL/ER-3 UC-408 Argonne National Laboratory (1994).

25 Rundo, J, Keane, A T, Lucas, H F et al . Current (1984) status of the study of 226Ra and 228Ra in humans at the Center for Human Biology. In Proc. Symp. "The Radiobiology of Radium and Thorotrast". Eds. W. Gössner, G B Gerber, U Hagen, A Luz. Neuherberg 29 31 Oct, 1984. Strahlentherapie 80 Suppl. 14 21 (1986).

26 Shimizu, Y, Kato, H, and Schull, W J. Studies of the Mortality of A-Bomb Survivors. 9. Mortality 1950-1985. Part 2. Cancer Mortality Based on the Recently Revised Doses (DS86). Radiat. Res. 121: 120-141 (1990).

27 Shore, R E, Woodard, E, Hildreth, N, Dvoretsky, P, Hempleman, L, and Pasternack, B S. Thyroid tumours following thymus irradiation. J. Natl. Cancer Inst. 74, 1177-1184 (1985).

28 Shore, R E, Hildreth, N, Dvoretsky, P, Anderson, E, Moseson, M, and Pasternack, B. Thyroid cancer among people given x-ray treatment in infancy for an enlarged thymus gland. Am. J. Epidemiol. 137, 1068-80 (1993).

29 Spiess, H. The Ra-224 Study: Past, Present and Future. In: Proc. Int. Seminar on Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium, pp.157 113. Eds. G van Kaick, A Karaoglou and A M Kellerer. World Scientific, Singapore (1995).

30 Stewart, A M, Webb, J, and Hewitt, D. A survey of childhood malignancy. Br. Med. J. I: 1495-1508 (1958).

31 Stewart, A M, and Kneale, G W. Radiation dose effects in relation to obstetric x-rays and childhood cancers. Lancet i, 1185-1188 (1970).

32 United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionising radiation. 1977 report to the General Assembly, with annexes (1977).

33 UNSCEAR. Ionizing Radiation : Levels and Effects. 1972 Report to the General Assembly, with annexes. Vol. II: Effects. New York, United Nations (1972).

34 UNSCEAR. Ionising Radiation : Sources and Biological Effects. 1982 Report to the General Assembly, with annexes (1982).

35 UNSCEAR. Genetic and Somatic Effects of Ionising Radiation. Report to the General Assembly, with annexes (1986).

36 UNSCEAR. Sources, Effects and Risks of Ionizing Radiation. 1988 Report to the General Assembly, with annexes (1988).

37 UNSCEAR. Sources, Effects and Risks of Ionizing Radiation. 1993 Report to the General Assembly, with annexes (1993).

38 UNSCEAR. Sources, Effects and Risks of Ionizing Radiation. 1994 Report to the General Assembly, with annexes (1994).

39 van Kaick, G, Muth, H, and Kaul, A. The German Thorotrast Study. Report No. EUR 9504 EN. Luxembourg CEC (quoted in BEIR IV) (1984).

40 van Kaick, G, Wesch, H, Luehrs, H, Liebermann, D, and Kaul, A. Epidemiological results and dosimetric calculations - an update of the German Thorotrast Study.. In: Proc. Int. Seminar on Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium, pp.171-175. Eds. G van Kaick, A Karaoglou and A M Kellerer. World Scientific, Singapore (1995).

41 Yoshimoto, Y, Kato, H and Schull, W J. Risk of Cancer among children exposed *in utero* to A-bomb radiations, 1950-84. Lancet 2: 665 (1988).

42 Yoshimoto, Y, Delongchamp, R, and Mabuchi, K. In utero exposed atomic bomb survivors: cancer risk update. Lancet 344: 345-346 (1994).

Table 1
Numbers of deaths from all cancers other than leukaemias among Japanese atomic bomb survivors with a DS86 dose of 0.75 Gy or more (from Preston and Pierce, 1987)

Age at Exposure		Time since exposure (years)		
		5-25	25-40	5-40
<20	O[a]	14	44	58
	E[b]	4.03	17.8	21.8
	O/E[c]	3.47	2.47	2.66
20-34	O	26	58	74
	E	13.0	24.4	37.4
	O/E	2.01	1.96	1.98
35	O	119	99	218
	E	86.7	68.9	155.6
	O/E	1.37	1.44	1.4
All	O	159	191	350
	E	103.7	111	215
	O/E	1.53	1.72	1.63

[a]O - Observed number of deaths

[b]E - Expected number of deaths in a unirradiated population, based on rates among those with a DS86 dose <0.1 Gy

[c]O/E - Relative risk

Table 2
Human populations available for risk estimation

Atomic Bombs	Japanese Survivors Marshall Islanders[a]
Medical Diagnosis	Multiple Fluoroscopies (breast) Prenatal Irradiation Thorotrast Injections[b]
Medical Therapy	Pelvic Radiotherapy (cervix) Spinal Radiotherapy (ankylosing spondylitis) Neck and Chest Radiotherapy (thyroid) Scalp Radiotherapy Radium Treatment[b]
Occupational Exposure	Uranium Miners Radium Ingestion (dial painters)[b]

[a] exposure to external radiation and / - emitting radionuclides
[b] exposure to -emitting radionuclides.

Table 3
Summary of dose and dose rate effectiveness factors

Source	DDREF
ICRP 1977	2.5
NCRP 1980	2 - 10
UNSCEAR 1986	up to 5
UNSCEAR 1988	2 - 10
BEIR 1990	2 - 10
ICRP 1990	2
NRPB 1993	2
UNSCEAR 1993	<3

Table 4
Estimated lifetime fatal cancer risks in populations (all ages, both sexes) associated with exposure to low LET radiation at high doses and high dose rates, based on a multiplicative projection model

Population		Fatal cancer risk 10^{-2} Sv^{-1}
UNSCEAR 1977	-	2.5[a]
UNSCEAR 1988	Japan	7 - 11[b]
BEIR V 1990	USA	7.9[c]
ICRP 1991	Five nations	10.0[d]
Muirhead 1993	UK	4.9 - 11.8

a additive model
b range based on age-averaged and age-specific constant relative risks
c see text (Section 5.2)
d average value based on US, UK, Japan, Puerto Rico and Chinese populations. Risk for workers 8.0 10^{-2} Sv^{-1}
e risk calculated to 40 years after exposure and lifetime assuming age-specific relative risks. Risk for workers 5.9-10.1 10^{-2} Sv^{-1}.

Table 5
Risk coefficients for fatal cancer adopted by ICRP

Organ or tissue	Fatal cancer, 10^{-2} Sv^{-1}		
	ICRP 1977	ICRP 1991	
		Population	Workers
Bladder		0.30	0.24
Red bone marrow	0.20	0.50	0.40
Bone surface	0.05	0.05	0.04
Breast	0.25	0.20	0.16
Colon		0.85	0.68
Liver		0.15	0.12
Lung	0.20	0.85	0.68
Oesophagus		0.30	0.24
Ovary		0.10	0.08
Skin		0.02	0.02
Stomach		1.10	0.88
Thyroid	0.05	0.08	0.06
Remainder	0.50	0.50	0.40
Gonads (hereditary disease)	-	-	-
Total	1.25	5.0	4.0

Table 6
Risk Factors for Protection, 10^{-2} Sv^{-1}

	ICRP 1977	ICRP 1991	
		Public	Workers
Fatal cancer	1.25	5.0	4.0
Hereditary defects	0.4[a]	1.0[b]	0.6[b]
Total	1.65	6.0	4.6
Total (weighted)[c]	-	7.3	5.6

[a] two generations
[b] all generations
[c] to allow for non-fatal cancers and years of life lost for cancers and hereditary disease.

Figure 1:
Dose-response relationship for radiation-induced cancer. Possible inferences are illustrated in extrapolating data available at high doses and high dose rates to response at low doses and dose rates for low-LET radiation.