361. Although there are difficulties in estimating doses and in other aspects of these studies, risk appears consistently to increase with increasing dose and to decrease with increasing age. The bulk of the information suggests that the dose-response pattern is linear, although one Canadian fluoroscopy series has obtained a better fit with a quadratic model [H6]. Radiogenic breast cancers occur at the same ages at which breast cancers occur naturally; elevated risk appears to persist throughout life, after an initial latency period. Latency is rather long (> 10 years); it may also vary, being an inverse function of age at exposure. In general, cases of exposure at postmenopausal ages have not been studied in numbers sufficient to allow a reliable assessment of effects, and there may be a decreased susceptibility with increasing age [T14]. However, exposed Japanese of this age have a relative risk of 3.1 [L6, T6, T14]. The possibility of a cohort effect, associated with the increase in breast cancer in Japan since 1945, should be considered. As discussed earlier, it has now been shown that exposure at ages below 10 leads to a substantial risk of breast cancer.

362. The details of the relative risk of breast cancer from incidence data collected in Hiroshima and Nagasaki for the period 1950-1980 are summarized in Table 35 [T14]. A trend of increasing susceptibility with decreasing age, within a given dose level, can be seen. Figure X shows the decrease in relative risk with increasing age at exposure, for the 0-0.09 and the 0.5+ Gy (T65) groups [T14].

363. The Japanese results can be compared with those of two other studies from the United States, a Massachusetts tuberculosis fluoroscopy and a Rochester series of post-partum mastitis patients [B2, C4, L6, S47]. Howe has also reported fluoroscopy data from most provinces in Canada [H6]. Total relative risks, for doses from 1 to 4 Gy, are consistently between 2 and 3, with values of 4-6 for those exposed at younger ages. At doses higher than 4 Gy, most studies have only small samples; however, the largest of these has found a relative risk of 14.6 at high doses [H6]. Incidence data from Japan suggest a corresponding relative risk of about 4 [W5], indicating perhaps that survival from breast cancer depresses the true relative risk estimated from mortality data. Relative risk data from these four study populations are summarized in Table 36. Table 37 provides details on relative, as well as absolute, risk differences for three of the major investigations, subdivided according to age at observation and age at exposure; the similarities in the different data sets can be seen.

364. A recent case-control study of breast cancer following irradiation to treat tuberculosis in Denmark has found no significant increase [S53]. While the study was too small to rule out an effect, it was large enough to confirm that other studies in the literature are not underestimating the risk. A similar negative result, and interpretation, has also been reported by Davis et al. [D27] based on a study in Massachusetts. Doses were smaller than in other series (0.66 Gy) and the average age at exposure higher (28) than in other studies.

365. Acute post-partum mastitis patients have now been followed for up to 45 years, with an average follow-up time of 29 years [S47]. Relative to controls and female siblings of patients, the RR value for breast cancer in the irradiated breast, age and interval-adjusted, is 3.2 (90% CI: 2.3-4.3). The risk increased by 40% per Gy with an essentially linear dose-response except for a diminution at doses above 7 Gy, with no fractionation effect. A multiplicative projection model was a better fit than an additive one, and the RR did not change with time since exposure.

366. The absolute risk in Japan has been estimated to be between 3.0 and 4.0 ± 0.7 cases per 10^6 PYGy, with a pattern that is roughly linear and no inter-city difference [T9, T14]. Risk coefficients in the various fluoroscopy and mastitis series range from 6 to 8.5 cases per 10^4 PYGy [C4]. As previously noted, with the exception of the Nova Scotia series, these data are consistent with a linear dose-response pattern (see Figure XI and Table 38). The New York mastitis data for uni-lateral breast exposure suggest that doses of 4-14 Gy have a cell-killing effect [B2, C4, L6]. However, for bilateral breast exposure, even at higher doses (in some instances tens of Gy) no downturn in the dose-response curve was observed. The fluoroscopy series, especially in Nova Scotia, were highly frac-

![Figure X. Relative risk of breast cancer in atomic bomb survivors for the 0.5 or more Gy relative to the 0-0.09 Gy dose group (T5EDR kerma doses).](T14)
tionated, and this may make a difference at high doses. Mastitis may also have its own biological relationship to breast cancer after irradiation [L6].

367. Besides the slight indication of non-linearity at high doses in [S47], the other exception to a simple linear model is from a record-linkage study of data from nearly all of Canada. A pure quadratic model appears to fit these data best, though a linear-quadratic model fits almost equally well [H6]. The departure from linearity is evident in the lower response per unit dose of women in the Canadian provinces other than Nova Scotia, where the doses ranged up to much higher values [H6]. In Nova Scotia, the patients were examined in the anterior-posterior position (facing the x-ray tube) whereas in the provinces the patients were mainly examined in the reverse position, resulting in doses per fraction about 20 times smaller. The absolute risk on a linear basis in the range 0-2 Gy, which contains the major fraction of the cancer cases, appears to be about three times smaller for those provinces than for Nova Scotia alone. Based on the evident lack of excess cancer for the lower dose range (0 to 0.99 Gy) in the Canadian study as a whole [H6], this factor would be considerably greater at low doses. This one series contributes the bulk of the data above 4 Gy. Howe argues that because in other instances high-dose information is relatively sparse, and because it is in the high dose range that non-linearity is expected to be most apparent, a linear-quadratic model is the prudent model to adopt in the establishment of breast-cancer dose-response patterns [H6].

368. Two studies have examined the possibilities of synergism between several other risk factors in women irradiated for post-partum mastitis [B30, S37]. These factors include family history of breast cancer, late age of parity, oral contraceptive use, menopausal hormone use and various ovarian-related factors. Women with benign cystic breast disease and those irradiated at the time of their first childbirth were at increased risk, but other women were not.

(iii) Lung

369. Most of the exposures to the breast or chest also involve the lung, and there are several cohorts of individuals who received internal exposures specifically to the lung, principally underground miners who inhaled radioactive radon gas. Exposures to the lung from therapeutic radiation have been experienced by patients with ankylosing spondylitis. These and the other groups have experienced most of the kinds of exposures needed to understand the radiosusceptibility of the lung. In particular, the miners were exposed to moderate doses of high-LET radiation over long time periods, the atomic bomb survivors were exposed to a single dose, and the radiotherapy patients received fractionated, moderate-to-large doses over a short time period.

370. There appear to be no risk differences between males and females, after accounting for the effects of smoking. Most of the available information, however, comes from males; data on both sexes come primarily from Japan and clearly suggest no difference except that which is due to smoking [S49].
371. Relative risks from exposures to brief external x- and gamma-irradiation are 1.2-2.0 [K7, S28, S31, W5]. In the miners, who had variable levels and durations of exposure to inhaled alpha radiation, because relative risks are dose- and duration-dependent and because there may be interaction between the exposures and smoking, this aspect of the data will be discussed in section V.A. The mining data come from uranium miners in Czechoslovakia [S19, S51], the United States [C20, I11, S20] and Canada [C4, G10, H15, M19]; from Swedish metal and Canadian gold miners [A9, D12, E1, M19, R5, R7]; and from a few other reports [C4, R7, T11, T20]. Thorotrast patients were exposed to thoron (²²⁶Rn) gas, also an alpha-emitter, as an exhalant; these patients manifest an excess of lung cancer (40 cases vs. 34 expected) after doses ranging from 0.3 to 14 Gy [K16]. The smoking habits of these patients do not differ from those of the general population of the Federal Republic of Germany.

372. Radiogenic lung tumours appear preferentially in the epithelium of the upper bronchial tree, unlike in experimental animals given radioactive inhalants or intratracheal instillation. One mechanism for the upper bronchial effect of natural exposures to radon daughters is the adsorption of the free-ion fraction, that is, ions not bound to dust particles (see Annex G of the UNSCEAR 1977 Report [U2]). Most data suggest that the cell types do not significantly differ from those in non-radiogenic lung cancer [C4, C12, S20].

373. The ages of onset of radiogenic lung cancers are similar in general to those of spontaneous lung cancer; there is little evidence for excess risk before age 35 [C4]. This suggests that the latency period is a function of age at exposure; however, not all of the data are consistent. The minimal latency period has usually been at least 10 years, roughly independent of age at exposure in spondylitis patients and in Swedish [R5] and Canadian miners [C4]. In other mine studies and in the Japanese atomic bomb survivors, latency has been dependent on, and negatively correlated with, age at exposure: early exposure has led to longer latency and, perhaps as a result of increased years at risk or increased years at observation, higher absolute or lifetime excess risks. The data from the United States are not entirely clear. In one study of Colorado miners (where dose rates may have been higher than elsewhere), there was a shorter latency period in exposed smokers than in non-smokers, but doses may have been overestimated due to the way in which exposures were sampled [C4, R5]. Moreover, the follow-up times for individuals initially exposed at younger ages may be insufficient. Excess risk is known to persist for at least 50 years after exposure began.

374. The overall data suggest that the relative biological effectiveness (RBE) of alpha-radiation to the lung relative to gamma-radiation, is 20, although there is much uncertainty in this estimate, largely ascribable to the difficulty of converting data on WLM to absorbed doses in Gy [C4]. A reference conversion is 6 mGy per WLM for mean bronchial dose and usual conditions in mines [I11]. This results in unit risk of 1.0 per 10⁴ PY-WLM corresponding to 1.67 per 10⁴ PGy.

375. Thomas and McNeill have fitted the dose-response data to additive and multiplicative models for exposure to alpha-emitting radionuclides [T11, T20]. Results are provided in Table 10. The models fitted were linear cell-killing models of the form (using their notation)

\[ R = (a + bD)^{\gamma(0.5)} \]

where \( a, b, c \) and \( d \) are the parameters estimated from the dose-response relationship, fitted by weighted least-squares, and \( R \) refers to both additive and relative risk (in the case of additive risk, \( a \) was set at 0.0, and in the case of relative risk, to 1.0). The second exponential term models cell-killing effects. A linear dose-response is modelled by setting \( c = 1.0 \). For details on the justification of this dose-response model, see [T11, T20]. Thomas and McNeill found some evidence of a departure from linearity in the dose-response patterns of the mining data (Figure X11).

376. An extensive analysis of lung cancer in miners exposed to radon daughters has been published, reporting on results from four studies of six miner groups in Czechoslovakia [S51]. The lung cancer rate increased as a function of exposure. Excess risk appeared about 5 years after the onset of exposure, peaked at 20 years, and, though excess persisted, it was no longer significant after 30 years (the approximate limit of follow-up to date in these subjects). Unlike some other studies of miners who began exposure under age 30, there was a detectable excess risk before age 40. However, relative risks were higher with greater age at onset of exposure. The data from the Czechoslovakian uranium miners appear to be essentially complete for group S (miners first exposed between 1948 and 1957) [S51, K28]; the total lifetime risk can thus be calculated directly without the use of a projection model, suggesting an average lifetime risk of approximately \( 4.5 \times 10^{-4} \) per WLM. Other findings of importance were: (a) a documented excess of lung cancer at total exposures less than 50 WLM; (b) an approximately additive effect of smoking; and (c) possible evidence for a cell-sterilizing effect at high doses for small cell lung carcinoma, but not for epidermoid cancers.

377. Further data on the Ontario miners have also become available [M40, M42]. These too indicate that the minimum latency period for appearance of excess lung cancers after first exposure to high concentrations of radon daughters is 5 years, not 10 years as previously assumed. This conclusion is substantiated by studies of the Eldorado uranium miners in Canada [H25, H31]. It also appears that excess lung cancers in these uranium miners reached a maximum about 10-15 years after first exposure and decreased towards zero about 20 years after last exposure [K28, M40, S51]. The risk coefficient derived from the Ontario miners study suggests an average lifetime risk of about \( 1.7 \times 10^{-4} \) per WLM for miners exposed to 1 WLM per year from age 20 to 55.

378. The range of risk coefficients derived from various studies of uranium miners is very broad but is
in general compatible with the central value of about 10 excess cancers per 10^4 PY and WLM (additive risk model) or about a 1% increase in normal incidence (as suggested in ICRP 50) of lung cancer per WLM (multiplicative risk model). When applied to the adult male population of North America, these risk coefficients suggest an average lifetime risk of about 3 \times 10^{-4} per WLM for uranium miners age 20 to 55 at the time of exposure [M40]. Recent data from those studies in which most attention was given to reassess exposure data are compatible with the range of 1.5-4.5 \times 10^{-4} per WLM for adult male miners, as was estimated in ICRP 32.

380. In an initial study from Sweden, Svensson et al. reported on a case-control study of the association between lung cancer and radon in houses in the area around Stockholm [S32]. Study subjects had lived in the area for 30 years or more. There was a statistically significant relative risk of 2.2 (95% CI: 1.2-4.0), and 4.1% of cases in this group appeared to be attributable to the exposure. There was an indication of a dose-response pattern, with increasing cumulative exposure, as seemed similar to results from miners in the United States and in Czechoslovakia.

381. Other data have not shown an effect of domestic radon daughter exposure on lung cancer. A recent study by Gjorup and Hansen [G20] compared Denmark to Sweden, which has 2.1 times the radon exposure levels.
in homes. There was no evidence for an excess of lung cancer in Sweden. Potential differences in other risk factors, such as smoking, were not studied in this report.

382. The ICRP issued in 1987 a summary of the risks associated with exposures to radon [111]. This study covered the existing literature in detail up to about 1986, and considers many aspects of exposure of the lung to high-LET radiation. Its conclusions and lifetime risk projections are given in chapter VII.

383. The BEIR IV Committee [C20] has recently issued an appraisal of the effects of radon exposure. This report was received too late for review by UNSCEAR, and only a brief Secretariat review is considered here. The BEIR IV Report reviews all of the high-LET data available to it through 1987, for all types of exposure, and provides extensive dose-response modelling and statistical fitting, as well as lifetime risk projections.

384. After reviewing the literature on radon, the BEIR IV Committee considered the best way to obtain a single numerical estimate of the risk from radon exposure is with the following equation:

$$r(a) = r_0(a) \left[ 1 + 0.025g(a)(W_1 + 0.5W_2) \right]$$

where $r(a)$ is the lung cancer mortality rate at age $a$; $r_0(a)$ is the baseline lung cancer mortality in the United States 1980-1984 population; $g(a)$ is a coefficient equal to 1.2 for ages less than 55 years, 1.0 for ages 55-64 years, and 0.4 for ages 65 years and over; $W_1$ is the cumulative radiation exposure in WLM from five to 15 years before age $a$; and $W_2$ is the cumulative exposure 15 years or more before age $a$. This is a relative risk model which accounts for age at risk.

385. The BEIR IV Committee [C20] considered only occupational data. On the assumption that the occupational results can be applied to radon exposures in houses, BEIR IV estimated that 1 WLM per year would increase the number of lung cancer deaths in both sexes by a factor of 1.5 with current patterns of cigarette smoking. Occupational exposures to 4 WLM per year from ages 20-40 were estimated to increase the male lung cancer deaths by a factor of 1.6, most of the cases being in smokers. Note, however, that the exposure estimates for two of the studies used for the calculations done by the BEIR IV Committee, notably the Beaverlodge data [H25] and Swedish iron miners [R5], have been questioned by Frost, and Swent and Chambers (see [C20]). It has also been argued that a large part of the difference in risk estimates for the general population is due to differences in the assumed lung cancer rates in the reference populations rather than to differences in the risk coefficients in BEIR IV [C20] and ICRP 50 [111]. The BEIR IV Committee modelled the smoking data as interacting multiplicatively with radiation, but acknowledged that a sub-multiplicative (but not additive or sub-additive) model was consistent with the existing data.

(iv) Thyroid

386. The best data on thyroid cancer are from children irradiated for a variety of conditions; these have already been reviewed (paragraphs 206-216). Adults have been treated with radioactive iodine for hyperthyroidism, without showing any documented excess of true thyroid cancer [C4, H12, H14]. In adults as in children, the anaplastic, and highly dangerous, form of thyroid cancer apparently has not occurred following irradiation.

387. A recent report has examined thyroid cancer in adults as well as children exposed to fallout from the Nevada, United States, atomic test site [Z3]. No excess was observed, and it is apparent that very large samples would be required to detect such an excess. The doses received by the Nevada population are in the range 0-1.5 Gy, usually below 0.4 Gy in adults. Based on these and other data, including the risk to the thyroid from external x-rays, the authors estimated the absolute excess risk to be between one and four cases per 10^4 PYGy. The BEIR estimate was four carcinomas per 10^4 PYGy, including some occult carcinomas [C4]. There is insufficient information on which to base estimates of the effect of age at exposure.

388. Two reports from Sweden have examined thyroid cancer in adults and to a smaller extent in children following the administration of diagnostic amounts of I-131 which delivered doses to the thyroid gland of 0.5-1.5 Gy at dose rates of 2-6 mGy per hour [H27, H28]. In the first and preliminary study [H27] the incidence of thyroid malignancies in about 10,000 patients receiving typical administrations of 2 MBq was compared with the expected number of malignancies computed from the age- and sex-specific incidence in the Swedish Cancer Registry. Eight cases were found in the patients after a follow-up of 17 years compared with 8.3 expected. The authors estimated that an excess of at least 16 would be expected based on risk estimates for adults in the Japanese atomic bomb survivor population (external acute low-LET irradiation). This study was analysed further in a report of the United States National Council on Radiation Protection and Measurements [N5] which concluded that a risk reduction factor of at least 3 was applicable to iodine-131 irradiation compared with high dose rate external irradiation. Another review of this study is contained in the UNSCEAR 1986 Report (U1) which points out several factors which might account for the failure to observe the predicted excess.

389. The above study has recently been expanded [H28] to 35,000 patients receiving diagnostic I-131 administrations with a mean absorbed dose of 0.5 Gy, followed for an average of 20 years. Again the incidence of thyroid malignancies was compared with the expectation based on Swedish Cancer Registry data. Record linkage identified 50 thyroid cancers occurring 5 or more years after the initial I-131 administration compared to 39.4 expected based on general population rates. Patients who were examined for a suspected thyroid tumour received the highest doses and were at the highest risk. Patients given I-131 for other reasons were not at increased risk and neither were those who were observed for 10 years or more. An expected excess of 41 thyroid cancer cases was computed from the age- and sex-specific risk
coefficients estimated by the United States National Institutes of Health, Committee on Radioepidemiologic Tables for external high dose rate irradiation by x or gamma rays [U4]. The authors concluded that the thyroid cancer risk from irradiation of the thyroid gland by $^{131}$I might be up to four times lower than with acute external low-LET radiation.

390. An excess of thyroid cancer has occurred in Japan [C4]. The approximate estimate for both cities, based on T65 doses, is 0.92 male and 2.40 female cases per $10^4$ PYGG [C4]. Relative risks have been about 4, with the excess appearing 15 years after the bombing and persisting thereafter: whether risk has begun to decline is not certain. Generally, the adult pattern is similar to the pattern in children, with latency and subsequent risk behaving as they do for other adult epithelial tumors. Despite the difference in the absolute risk of spontaneous thyroid cancer between males and females, the 3:1 female to male case ratio is about the same as that in the unexposed population.

391. A recent summary of thyroid cancer risks issued by the National Council of Radiation Protection and Measurements [N5] expressed risk as follows:

$$\text{Risk} = R \times F \times S \times A \times Y \times L$$

where R is the absolute risk per $10^4$ PYGy for both sexes in ethnically similar populations of children exposed to external x-irradiation after a minimum induction period of five years. For the United States population, based on estimates derived from externally irradiated children, the report [N5] takes this value to be 2.5. F is a dose-effectiveness factor equal to 1.0 for external x- or gamma-irradiation and for $^{129}$I, $^{139}$I and $^{131}$I and equal to 1/3 for $^{131}$I and $^{129}$I. S is a sex-correction factor equal to 4/3 for females and 2/3 for males, assuming that females are twice as susceptible as males and that the value R is based on populations comprising equal numbers of males and females. A is an age-susceptibility correction factor equal to 1 for exposure at ages under 18 and 1/2 for exposure at older ages. (If sex-specific R values are used, then S = 1.0). Y is the average number of years of post-exposure risk in the group being evaluated. L is lethality, equal to 0.10, assuming that only 1 case in 10 is lethal (this factor is to be used only when estimating the lifetime deaths due to radiogenic thyroid cancer).

392. The risk can be calculated for any study group using this formula. As an example, Table 39 provides risk estimates for an exposed United States population [N5]. The report of the National Council on Radiation Protection and Measurements compared absolute and relative risk models and found little difference in lifetime estimates. This model was also tested against the Marshallese data, from which direct estimates of risk are not reliable, and it gave an adequate fit [N5].

(v) Other epithelial tissues

393. The literature on lung, breast, and thyroid cancers has been reviewed separately because, of all epithelial cancers, these are the ones for which the best data are available. There are, however, many other epithelial tissues in the body. Data on cancer in these tissues come mainly from three groups of individuals; namely, the atomic bomb survivors, the ankylosing spondylitis patients and women irradiated for malignant and benign gynaecologic disorders.

394. For many years it had been thought that some organs were relatively insensitive to radiation carcinogenesis. This notion stemmed from the lack of evidence for a statistically significant excess risk or to the low background risk of the malignancy itself. It now appears that most (indeed, probably all) organs are vulnerable to radiation-induced cancer, given the right conditions of exposure. In Japan, data still do not support an excess risk or dose-response for cancers of the buccal cavity, rectum, pancreas, small intestine, uterus or malignant lymphoma [P15]. These sites may achieve significance as the exposed cohort passes through the years of greatest background risk, since in the last decade several sites not previously thought to be affected have shown a dose-response relationship. In patients irradiated for benign gynaecologic disorders, tumours of the buccal cavity, as well as of the kidney and urinary bladder, have relative risks of about 2, which are comparable to the relative risk in high-exposure Japanese (> 1 Gy) [W5] and in spondylitis (average exposure 2 Gy).

395. In their comparison of the data from Japan and the spondylitis patients, Darby, Nakashima and Kato have suggested that there may no longer be any truly radio-insusceptible epithelial tissues. This opinion is set forth in [D11] and [D20]; the latter contains the data on which the computations were based. Their conclusion was arrived at only when the data from the two groups were combined and analysed jointly, increasing the sample sizes sufficiently to show statistically significant excesses. A summary of the risks based on this joint analysis is given in Table 40. For example, gallbladder cancer was significantly more frequent than expected in the combined series than in either series alone. Darby et al. also described an excess of central nervous system tumours in their combined analysis, but see [P15]. This joint analysis will be referred to in the following paragraphs. However, it should be noted that these estimates, while they are the only joint estimates currently available and the only estimates based on a sample size large enough to detect significance for some sites, are based on obsolete doses and a shorter follow-up than is now available. The estimates have been revised recently, and while no new joint analysis is available, the revisions will not reduce the qualitative evidence for excess risk at the sites reported by Darby et al.

396. In addition to the cervical cancer patients, several other cohorts totalling about 14,000 women exposed to pelvic irradiation for a variety of benign gynaecologic conditions have been followed [B6, C4, S3, W6]. While these women add information on epithelial sites, they also pose further questions and uncertainties. Relative risk data for them were presented in Table 25. Both radium and x-ray treatments were involved [B12, D9], and the exposures were external, low-LET (x-ray) and internal, high-LET [W6]. Doses ordinarily ranged from 20 to 70 Gy, given in fractions of a few Gy over periods of 4-8 weeks [B12].
In women treated for benign disorders, uterine sarcomas were increased about eightfold and female genital and urinary organ tumours about twofold. Exposure to radiation may lead to relatively advanced, aggressive uterine tumours when the original reason for pelvic irradiation is to treat a malignant, rather than a benign, condition [M35]. An elevated risk of uterine sarcomas was seen in one ovarian cancer series [R11] but not in another [C8] nor in the cervical cancer series [B12].

The joint analysis of the Japanese data and the spondylitis data [D11, D20] (see Table 40), serves to summarize the available literature on a variety of exposed sites. A multiplicative projection model describes the combined data reasonably well. Age-specific relative risk is roughly constant as a function of age once the latency time is over. For heavily irradiated sites, both sets of data show a positive correlation between the excess risk and the baseline prevalence of the tumour (Figure XIII). This correlation suggests that radiation magnifies processes already at work multiplicatively.

In their analysis of the Life Span Study data for the years 1950-1978, Kato and Schull [K7] concluded that the mortality experience of this cohort supported a relative risk model more strongly than the additive one. This assessment has been further supported by the more formal adoption of the relative risk model in the Life Span Study Reports 10 and 11 [P15, S49]. Muirhead and Darby reached similar conclusions [M36, M37]. The excess deaths from all cancers other than leukaemia and bone cancer increase with age at death for the same age cohort in proportion to the age-specific death rate from cancers in the population of all Japan and do not show a constant excess value by age at death for the same age cohort, as predicted by the absolute risk model.

Darby et al. also examined the post-exposure risk for a pooled series of selected epithelial sites for which data are available from both the spondylitis series and the $>1$ Gy group in Japan [D11, D20]. These sites, which the authors referred to as "selected sites", include the pharynx, oesophagus, stomach, pancreas, larynx, lung, ovaries, skin, and bones. They
also found that the relative risk model describes the data on the pooled sites.

401. However, the latest report from the ankylosing spondylitis series [D21] differs somewhat from the other data in regard to epithelial cancers other than colon cancer. The authors have found that 25 years after irradiation, the RR values return approximately to normal, contrary to the essentially permanent effect seen in other studies. Age at irradiation did not significantly affect the subsequent relative risk for these tumour sites (no patients where such an effect has been seen were under age 15).

402. The relative risk is higher in females than males in Japan for many epithelial sites (it is lower for leukaemia). This is shown in Table 41, taken from Life Span Study 10 (T65). For oesophageal and lung cancer, the difference is probably due to different smoking habits.

403. Because differences have appeared between the Japanese and spondylitis study, and the doses have been revised, one must interpret the parallel analysis of Darby et al. with caution. However, the new data seem unlikely to change the support for the relative as opposed to the absolute risk model for excess solid cancer risk, even if the relative risk is found to be a function of sex, age at exposure, and time since exposure, as suggested by Muirhead and Darby [M36, M37]. Similarly, Darby et al. used pooled data to demonstrate excess cancer risk at many sites for which an excess could not be documented in either study alone. This is probably a reliable indicator that those sites are susceptible to cancer from exposures to ionizing radiation.

404. In analysing the available data on these epithelial tumour sites, especially those of the digestive system, a variety of observations are worth summarizing.

405. Digestive system. Little data exist on salivary gland tumours from Japan and the spondylitis series, partly because of the low exposure levels. However, from the essentially consistent results of eight studies of medical therapeutic exposures, Land [L11] estimates that the absolute risk of salivary gland tumours is 0.26 ± 0.06 cases per 10^4 PYGy after the first five years post-exposure, with little evidence of an association between response and age at exposure. The data are summarized in Table 42. Most of these exposures are in children, including two tinea capitis series [M13, S16], and head and neck exposures in five studies [H1, J4, M11, S15, S40], or in middle-aged women treated with radioactive iodine [H21]. In the Japanese data, dose estimation is complex, but the risk is estimated as 0.056 ± 0.036 per 10^4 PYGy for malignant salivary gland tumours and 0.063 ± 0.035 per 10^4 PYGy for benign ones [O4, T15]. Recent data have established the existence of a dose response for oesophageal cancer and for stomach cancer, but it is still difficult to obtain accurate estimates of the lower bounds of the effects [O3].

406. No single data set supports an excess for gallbladder cancer; the main risk factor for this very rare tumour is gallstones, which are relatively rare (but becoming more common) in Japan and more common in women. Most of the spondylitics were men; the gallbladder was given little dose in the cervical cancer patients. There is little statistical power in the available data, although the recent report [P15] from Japan estimated a small effect (relative risk at 1 Gy about 1.15).

407. The pancreas seems to be of uncertain susceptibility [L11]. Risk cannot be assessed from the available data, and expected rates are complicated by problems in late and sometimes difficult histologic diagnosis. In many countries pancreatic cancer is a common cancer, and one might therefore expect the evidence to more clear-cut; this is not the case at present.

408. Cancer of the small intestine is generally rare, and it is still difficult to know if there is a radiogenic effect. The data come mainly from some cervical cancer patients, but, as noted earlier, both irradiated and non-irradiated subjects had similar excesses. Colon cancer has already been discussed in the context of the cervical cancer patients, where inconsistent results were obtained. In Japan, mortality data show an increase in the Life Span Study sample using the T65 doses [K7, P15] and the new DS86 doses [S48]. Only a non-significant increase was reported in the spondylitics; however, a possible association between spondylitis and ulcerative colitis casts doubt on that result [D11]. Rectal cancer seems to be a consequence of exposure to ionizing radiation, but a dose-response pattern is not estimable and the dose may need to be more than 1 Gy to produce a detectable effect.

409. Genito-urinary system. The mortality data from Japan still do not support a dose effect for uterine or uterine cervix cancer, and the evidence comes almost exclusively from those women irradiated for gynaecologic disorders. The only evidence of the inducibility of prostate cancer comes from the Nagasaki Tumour Registry; considering all cases, including those discovered only at autopsy, the absolute risk is 2.1 cases per 10^4 PYGy based on a linear model [L11, W5]. This has not been confirmed, at least as yet, in the mortality data [S48]. Prostate cancer is a disease of advancing age, and most cases are not discovered clinically and would not be reflected in mortality data. Land speculates that a small radiogenic risk would be even less detectable in the much higher background prostate cancer rate in Europeans and North Americans [L11].

410. A recent study in Japan [T21] has shown a statistically significant dose-response pattern for both malignant and benign neoplasms of the ovary, with a latency period of at least 15-20 years.

(vi) Liver

411. Somewhat more detail is available for liver cancer after radiation exposure. The liver had been regarded as being relatively radio-insusceptible. However, the Japanese data have now revealed a slight increase in liver cancer, when "not otherwise specified" cases are included [P15, S49]. It bears mentioning that the liver is a common site of metastasis for other radiation-induced cancers, e.g., those of the lung, stomach and breast, and that death certificates will
commonly fail to distinguish between a primary and a secondary malignancy, particularly in the absence of supportive pathological information. The increasing use of radioisotopes for diagnostic liver scans or other radiotherapeutic purposes makes more data available and also underscores the importance of a better knowledge of the liver's susceptibility. The best data come from the Thorotrast patients (indeed, Thorotrast use was stopped in about 1955, when its liver carcinogenicity was discovered [M26]). Most cancers caused by this agent are bile duct carcinomas, hepatocellular carcinomas or angiosarcomas [C4].

412. Thorotrast data are reviewed in [C4], and details specifically from the Federal Republic of Germany series are in [K16]. The average dose to the liver from the 25 ml of alpha-emitting substance injected was about 0.25 Gy per year; about 65% of the amount injected was deposited in the liver. From these exposures, the risk estimate was about 300 liver cancers per 10^4 PGy [C4], projecting cumulative risk to the lifetime of the exposed cohort of individuals. For an average of 23 years at risk beyond the first 10 years in this group, the estimated risk rate coefficient was 13 liver cancers per 10^4 PYGy. Complicating this assessment were the conceivable effects of Thorotrast toxicity, on the one hand, and radiation-produced cell sterilization, on the other. Tumours began to appear about 10 years after initial exposure, and the period of elevated risk may have extended beyond 40 years [K16].

413. The cumulative incidence of liver tumours in the Federal Republic of Germany series is presented in Figure XIV, for different liver dose rates measured by x-ray film and whole-body counter assessment. Because deposited radioisotopes can be visualized and quantified on x-ray film, the dose-response pattern has been estimated for liver cancer. Risk as a function of time since exposure rises more steeply in the more heavily exposed [K16].

414. Data are also available from Japanese military patients treated with Thorotrast to diagnose war injuries [M29, M31]. In these patients the risk for hepatic cancer was 40.0 relative to a military control group and 22.2 relative to population-based controls; the relative risk in both cases was 1.3 (not significant) for other tumours, which included a variety of sites. After 35-43 years, there have been 50 hepatic tumours in 254 subjects, a cumulative incidence of 19.2%. Based on autopsies from these individuals, the mean dose rate for the individuals with hepatic cancer was estimated to have been 0.29 Gy per year, low-LET equivalent, with a mean total dose of about 9.20 Gy [K18] of this high-LET exposure, after a mean 36.1-year latency period.

415. Other individuals have been exposed to alpha-emitters deposited in the liver, particularly 239Pu, in the case of nuclear workers. The available data do not show an effect but are compatible with an effect no greater than 10 times that of Thorotrast [C4].

5. Occupationally exposed adults

416. As was noted earlier, studies of the effects of ionizing radiation on adults exposed in the course of their employment or military service have focused largely on radium dial painters and radiologists in the United States and the United Kingdom or on individuals engaged in nuclear weapons research and fabrication, in the activities of nuclear power stations, in the maintenance and outfitting of nuclear-powered naval vessels, primarily submarines, or in nuclear weapons tests. The findings on the radium dial painters and radiologists have been described elsewhere in this document; this section summarizes the findings of one large case-control study of radiological technicians [J5] and of the other studies of occupational, including military-service-related, exposure.

![Figure XIV. Cumulative Incidence of liver tumours in Thorotrast patients.](K16)
417. Jablon and Miller [5], in a study of 6,500 radiology technicians in the United States Army in the Second World War, found no statistically significant differences between them and a control group (6,826 medical, laboratory and pharmacy technicians) with respect to the frequency of individual sites of cancer or deaths from other causes. More specifically, for 174,500 PY of risk, they observed 12 leukaemia deaths (including one case of chronic lymphocytic leukaemia) among the radiological technicians and 7 among the controls (P = 0.12, one-tailed test). While the doses are uncertain, their exposures may have been 0.05-0.15 Gy per year, based on the experience of similar technicians at the Cleveland Clinic (United States) in 1953. Most of these radiology technicians did not pursue the same kind of work after they had left the Army, where their average stay had been less than 3 years.

418. Efforts have been made to determine whether individuals employed in the nuclear industry do or do not have increased risks of cancer. In 1978, for example, Najarian and Colton [N6], in a study of 1,722 death certificates for a variety of workers at the Portsmouth Naval Shipyard (New Hampshire, United States), found six deaths from leukaemia among the 146 former workers presumed to have been involved in activities where exposure could have occurred, whereas 1.1 deaths were expected. A subsequent retrospective cohort mortality study [R17] of all the workers at this shipyard failed to confirm the finding. Among three cohorts, (a) 7,615 nuclear workers (doses 0.01-0.91 Sv; mean 0.03); (b) 15,585 non-radiation employees; and (c) 1,345 with no measurable exposure, on whom vital status could be ascertained in 96% of cases, Rinsky et al. found no increased mortality for the exposed groups as contrasted with the other two groups, nor did they find evidence of a dose-response relationship within the exposed cohort. The standardized mortality rate (SMR) for leukaemia was 84 (95% CI: 34-174). As is true in many occupational settings, some uncertainty surrounds the actual doses involved: for years prior to 1974, the estimates are based on film badges, but for subsequent years, they are based on calcium fluoride dosimeters. A study of the employees of all of the nuclear shipyards in the United States, government and private, is presently under way. While it has not yet reported its findings, the study may eventually clarify the issue. Similarly in 1981, Austin and his colleagues [A16] reported a threefold increase in the frequency of malignant melanoma among the employees of Lawrence Livermore National Laboratory (United States). Again, a substantially larger, later cohort study of the workers at Los Alamos National Laboratory (United States) [A15] failed to support this. Among 11,308 employees, only six cases of melanoma were ascertained where 5.69 would have been expected based on age and sex-specific mortality rates (SMR = 105). In neither of these studies was evidence presented that the cases had received higher exposures than other employees.

419. The situation with respect to the employees at the Hanford Facility in the state of Washington, United States, is equally perplexing. Kneale, Mancuso and Stewart [K20] purported to show that a variety of malignancies, including multiple myeloma, are elevated among the workers at this laboratory, but a more thorough and statistically sounder study [O12] does not bear out their contentions, although it does find a greater frequency of multiple myeloma than expected. It should be noted that even this result rests on three cases. Whether this increase is, indeed, a consequence of exposure is therefore moot, but multiple myeloma has been found to be elevated among the atomic bomb survivors, presumably as a result of their exposure, and the effect could be real. More recently, Beral and her colleagues [B22], using standardized mortality rates, examined the causes of death among 39,456 individuals employed by the United Kingdom Atomic Energy Authority (UKAEA) between 1 January 1946 and 31 December 1979. They found mortality to be increased for only four causes of death, namely, testicular cancer (SMR 153: 10 deaths), leukaemia (SMR 123: 35 deaths), thyroid cancer (SMR 122: three deaths), and non-Hodgkin's lymphoma (SMR 107: 20 deaths), but in no instance was this increase statistically significant at the 5% level. The SMR for myeloma was 83 (95% CI: 36-163). Cumulative dose estimates are available for approximately half of these employees; few (84) had received a cumulative dose in excess of 0.5 Sv. Among the workers for whom there were dose estimates, prostatic cancer was the only cause of death clearly related to exposure (SMR 594 for employees with exposures exceeding 10 mSv; four deaths). Although the numbers are small and the evidence is perforce weak, the data suggest a greater risk among workers exposed to tritium than among workers exposed to other sources of ionizing radiation (SMR 889; 6 deaths). Beral et al. [B22] estimate excess mortality for leukaemia and all cancers were 2.2 and 10.5 deaths per 10^5 PYSv, respectively. Neither of these estimates is significantly different from zero, but at face value they both agree reasonably well with the Japanese and other studies. It is interesting to note that when the UKAEA findings and the Hanford findings are combined, neither the increase in prostatic cancer seen among the former nor the increase in multiple myeloma seen among the latter is any longer significant [D24]. This suggests that both individual findings could be due to chance.

420. Possibly the most thoroughly studied of these special cohorts has been the plutonium workers, particularly those individuals who were involved in working with this element at the time of the Manhattan Project, when the potential hazard associated with the inhalation of plutonium particles was poorly recognized. Some 37 years of follow-up have failed to disclose an increased frequency of any malignancy; the number of workers involved is small, but their exposures were undoubtedly large [V2]. Studies of plutonium workers at the Los Alamos facility [V3] as well as of workers at other installations in the United States [W18] have also failed to find a significantly elevated risk of malignancy, generally or site-specifically. Although the number of years at risk are already large, these studies continue, and it is conceivable that an effect could still emerge.

421. In 1979, a preliminary report [C16] indicated that eight cases of leukaemia had been identified
among 3,224 former servicemen who had participated in the nuclear weapons test code-named SMOKY, one of a series known as PLUMBBOB, conducted at the Nevada Test Site, United States, in 1957. Only 3.5 cases would have been expected on the basis of age- and sex-specific population rates (RR = 2.3). Subsequent studies of this same cohort [C7] extended the observations to the incidence of all types of cancer and other specified causes of death. No increase in other cancers was seen, but 10 cases of leukaemia (including one of chronic lymphocytic leukaemia) were found where 4.0 were expected (RR = 2.5). Similar claims, based largely on scanty epidemiological evidence, have since been made for Australian and British participants in weapons tests carried out by the United Kingdom [K21].

422. Stimulated by these reports, the Medical Follow-up Agency of the United States National Research Council launched an investigation of the participants in five series of tests occurring in the years 1951 through 1957 [R16]. This investigation embraced a cohort of 46,186 individuals. A total of 46 deaths from leukaemia were ascertained (52.4 expected on population rates). No significant excess was found among the participants at any test series other than PLUMBBOB or among PLUMBBOB participants not represented at SMOKY. The earlier findings of Caldwell and his colleagues with respect to the SMOKY test were confirmed. No other form of cancer was consistently elevated; overall, only 1,046 deaths from malignant neoplasms were identified where 1,243 were expected based on population rates (SMR = 0.84). While the doses of the individuals involved in all of these tests are poorly known, film badges suggest that the highest dose received by any one of the participants in SMOKY who subsequently succumbed to leukaemia was 0.036 Sv (most received doses of less than 0.005 Sv). At the present, then, there is no consistent or statistically significant evidence for an increase in either leukaemia or other malignant neoplasms in nuclear test participants.

423. Darby et al. [D26], updating the study of Knox et al. [K21], have summarized the cancer mortality and incidence among 22,347 men who participated in the United Kingdom’s atmospheric nuclear weapon tests and experimental programme, and have compared these findings with those on 22,326 individuals matched with the participants for age, type of armed service, rank (officers and other ranks; socioeconomic class for civilians), and the date of entry to the study. The latter individuals were drawn either from among servicemen who did not participate in the weapon test programme, or, for the civilians, from the roster of employees of the Atomic Weapons Research Establishment who had not visited a test location or attended tests in the United States. Thirty-eight causes of death were examined separately.

424. Mortality from leukaemia and multiple myeloma in the participants was slightly greater than would have been expected from national values, but it was substantially lower in the controls. However, the rates of leukaemia and multiple myeloma showed very little difference between groups characterized by recorded doses from external radiation. These authors cautiously concluded “Participation in the test programme did not seem, in itself, to have caused any detectable effect on the participants’ expectation of life, apart from possibly causing small risks of developing leukaemia and multiple myeloma.”

425. Rinsky et al. [R21] have described the results of a case-control study of lung cancer in civilian employees at the Portsmouth Naval Shipyard (United States). Their study involved 405 cases and 1,215 controls drawn from the roster of civilian employees matched on age, year first (last) employed, age at date first (last) employed, and length of employment. The distribution of cumulative radiation doses among the cases differed little from that among the controls save in the percent exposed to 0.01-0.05 Sv where the radiation-related excess was statistically significant. However, when exposures to asbestos and welding fumes were taken into account, the radiation-related risks at all levels of exposure were reduced, suggesting a greater exposure to these factors. This confounds the observed association between radiation and lung cancer. Analysis of mortality by time since exposure revealed no pattern of increase as latency increased. Data on cigarette smoking and socioeconomic status were not available. These authors conclude that their study does not preclude an association between lung cancer and exposure to ionizing radiation (at the levels obtaining among nuclear shipyard workers) nor does it provide evidence in support of such an association.

426. Checkoway et al. [C21] have described a historical cohort mortality study of 6,781 white male employees of the nuclear materials fabrication plant known as Y-12 at Oak Ridge, Tennessee, United States, in the years 1947-1979. Among monitored workers, the mean cumulative alpha-radiation dose to the lung was 0.082 Sv, and the mean cumulative external whole-body penetrating dose from gamma-radiation was 0.0096 Sv. Mortality excesses were seen for cancers of the lung, brain and central nervous system, but not for other sites of cancer nor other causes of death when the rates among workers were compared either to national or state rates. No dose-response trend was observed for mortality from cancer of the brain and of the central nervous system, but the rate ratio for lung cancer, based on contrasting workers receiving 0.05 Sv or more with workers receiving less than 0.01 Sv, was 4.60 assuming zero-year latency and 3.05 on a 10-year latency. These rate ratios are, however, based on only three deaths and one death, respectively. Thus, the evidence of an increase in lung cancer mortality at these dose levels is far from compelling.

427. Workers for British Nuclear Fuels at the Sellafield plant have been studied [S54]. Among 14,327 known to have been employed at the plant from 1947-1975, 572 of 2,277 deaths were due to cancer, 5% less than expected based on death rates for England and Wales (overall mortality was also slightly less than expected). Radiation workers had deficits of liver and gallbladder cancers, lung cancer, and Hodgkin’s disease, and excess deaths from myeloma and prostate cancer. Neither excess was significant, and there was no excess in leukaemias. Dosimetry showed positive
associations between accumulated dose and death rates from bladder cancer, multiple myeloma, and haematopoietic neoplasms. These were significant in regard to doses accumulated up to 15 years prior to the time of death, but not if doses up to two years before death were included.

6. Exposures to elevated cosmic and terrestrial radiation

428. Although levels of exposure to cosmic radiation vary as a function of altitude, and although some correspondence exists between cancer rates and altitude, there have been few convincing studies to show whether cancer rates at high elevations are substantially different from those elsewhere [C4]. Many correlated factors could explain the data that are available (see [A5] for a review). Studies designed to assess firmly whether cosmic radiation itself causes cancer would require prohibitively large samples.

429. A large-scale investigation of background radiation has been undertaken in China [H24, Z4], where cancer mortality levels in a high-background area in Yangjiang country were compared to those in a control area with one third the exposure levels. After age adjustment, there were no significant differences, even though chromosomal and other indications of radiation exposure did differ.

430. A separate study has compared the effects of radon alpha-exposure in high-background areas of Guangdong Province of China [H24] with a control area. High-background area exposures were about 0.38 WLM per year, and control-area exposures were 0.17 WLM per year. No difference in age-adjusted lung cancer rates was found.

431. A study of total background radiation in Japan [U5] found an effect only for male liver cancer. This effect fitted a linear dose-response model, but it is difficult to determine if there were other factors correlated with background exposure or if the result is a statistical artefact of some kind, as one due to multiple testing. Liver cancer is not usually reported as a radiogenic site, unless doses are also high enough to induce excess cancer at most other sites as well. In Connecticut, United States, where there is a tumour registry and an airborne gamma survey of the entire state was taken, there was no association between terrestrial radiation and cancer in the period 1935-1974 [W16]. The authors concluded that even a population currently in excess of 3 million persons is too small to detect the level of excess risk which might be associated with the observed level of background radiation.

7. Summary of exposure effects in adults

432. In respect to the radiation exposure of adult human subjects (see also [B21]), several generalizations seem permissible. Regardless of the reason for the initial exposure, it is evident that: (a) a single exposure can be carcinogenic if the dose is large enough; (b) there is no uniquely radiogenic cell type; (c) though most, perhaps all, of the common cancers probably can be caused by ionizing radiation, until now the data have not shown a risk for chronic lymphocytic leukaemia, squamous-cell cervical cancer, or Hodgkin’s disease; (d) the breast, thyroid, and bone marrow are particularly susceptible; (e) leukaemia, especially acute non-lymphocytic leukaemia (ANL), can be produced by radiation; it has a latency period of less than 5 years, peaks rapidly thereafter and then declines, but some excess risk persists for at least 30-40 years; (f) solid tumours have an age-onset pattern similar to that of non-radiogenic tumours at the same sites after a latency of about 10 years. For many sites, the latency period is a function of age at exposure. In the existing studies, relative risks have been between 1 and 3 for many epithelial sites after many different kinds of exposures of about 1 Gy: risk persists for 30 years (for life, in some studies); (g) age at exposure is the most general host susceptibility factor, with higher risk associated with younger ages at exposure; (h) atomic bomb survivors and most other study cohorts have yielded comparable results, with a few notable exceptions, and the latter appear explicable in terms of the exposure regimens used and other factors; (i) some individuals may be genetically more susceptible to radiation-induced cancer than others, but good data to demonstrate this unambiguously are very limited.

IV. HOST FACTORS THAT MODIFY RISK

433. There are many biological differences among human beings that may affect their susceptibility to radiation-induced cancer. These biological variables are commonly known as host factors, referring to the risk that the exposed individual will become a host to a tumour. There are many possible host factors for which some data exist. Among these are (a) sex; (b) age at exposure; (c) genetic constitution; (d) health status; (e) life-style; and (f) ethnicity. Since the publication of the UNSCEAR 1977 Report, some information has become available on the potential role of each of the factors listed.

A. SEX

434. Current data generally suggest that sex has little or no effect on radiation carcinogenesis. Tumours in an irradiated population exhibit a sex ratio very similar to the same tumours in a non-irradiated population. There is a strong preference for females in thyroid cancers produced by radiation, but the sex ratio is similar to that observed for spontaneous thyroid cancer. So far, breast cancer following radiation has essentially been found only in females and this corresponds with the extreme rarity of male breast cancer. Cancers in the organs usually manifesting adult onset occur in the typical sex ratios, which for many sites (for example, the lung) show a male preference and there is no evidence that the radiation-related relative risk is higher. The male excess of lung cancer is probably a temporary one related to the history of smoking habits. Squamous cell carcinomas and adenocarcinomas of the lung in Hiroshima and
Nagasaki, for example, seem to develop more rapidly in males than in females, but no difference appeared after smoking habits were taken into account [H10, K22]. Adenocarcinomas are more frequently slow-growing than are lung cancers of other histology. The evidence of a slightly higher relative risk for females than for males in Japan at many epithelial sites was reviewed earlier (see Table 41); most of the difference is probably due to interaction with other sex-associated risk factors rather than to a radiation effect.

435. Radiogenic leukaemia in Japan has a similar relative risk in both sexes, although the excess risk per 10^6 PYGy is significantly less in females (1.95 in males and 1.20 in females). Background incidence of leukaemia is twice as frequent in males. For other fatal cancers, shown in Table 41, only multiple myeloma has a higher background incidence in females; however, the excess risks are, from a statistical standpoint, not significantly different in the two sexes. Since the background rates are higher in males, the relative risks are somewhat greater in females [P15]. Sex may influence tumour growth and, indirectly, survivorship.

B. AGE OF ONSET OF TUMOURS IN EXPOSED ADULTS: SINGLE AND CHRONIC EXPOSURES

1. Exposure to the atomic bombings in Japan

436. The carcinogenic effects of single exposures of external radiation are known almost exclusively from data in Japan. There, the relationships between dose, age at exposure and age at expression of excess risk have been studied in detail [K7, P15, S18, S48, S49, W5]. Because the results have been reviewed extensively elsewhere in this document, only those facts that relate to tumour sensitivity as a function of age at exposure and age of onset will be examined here. For most tumours, there is a decreasing sensitivity with increasing age at exposure, in terms of subsequent risk of excess cancer. The solid tumours of adult onset increase in frequency only at the ages at which they naturally appear in non-irradiated individuals. For leukaemia, the additive risk rises with age at exposure, while the relative risk declines rapidly with age over 10 [K7]. Leukaemia, a classic radiogenic tumour with other special characteristics, is usually treated separately. The characteristic pattern for breast cancer has already been discussed in relation to childhood exposures (see paragraphs 240-242). Basically, all tumour risks seem to decline as age at exposure increases. The same reports also show the positive correlation between risk and dose at all ages. There is an unexplained difference between the data in Japan and uranium miners, the latter showing increased risk with increased age at exposure [S51].

437. In addition to the fact that susceptibility to radiogenic tumours decreases with increasing age at exposure, the characteristic latency periods are related not so much to age at exposure as to the tissue involved. The leukaemias have the most definite pattern, with a latency of 2-5 years and a decline in additive risk after about 25-30 years; a similar pattern exists for bone cancer. However, the solid tumours of adult onset have latency periods of a decade or more, and the excess risk persists indefinitely, probably throughout life, although this will be determinable only after the entire cohort experience in Japan is known.

438. The subsequent risk of cancer fits a multiplicative risk projection model. The delayed latency period, the persistence of risk throughout adult years, and the age pattern of excess cases are all consonant with multi-stage carcinogenesis, as for example, the model proposed by Moolgavkar [M1, M2], which posits two stages with selective proliferation of partially transformed cells.

439. Under such a model, increased risk should be seen soon after exposure to a single dose, if (as seems likely) radiation acts as an initiating agent (see section III.A.1). However, if this effect is small in the contrasted groups, the excess risk will not be detectable for some time after it has actually arisen, given the available sample sizes. It can be shown that, under such a multi-stage risk model with multiplicative projection effects, because of the nature of the change in the risk function and the effects of competing causes of death (which effectively terminate the observational experience at age 85 or so), the mean age and the age distribution of cases in exposed adults will be similar to those in the population at large [M4]. For these reasons, the age patterns of risk for those exposed to single doses are in agreement with a multi-stage model, and no special life-history or tissue sensitivity characteristics are required, other than in those cases, e.g., breast, bone and leukaemia, where tissue life-history plays an obvious role in sensitivity.

2. Exposures to nuclear tests and fallout

440. The estimated dose-response pattern and its possible significance for those who have been exposed to fallout from a single nuclear detonation (adults in the United States and British military service, Japanese fishermen and Marshall Islanders) are discussed elsewhere in this document. In sum, the numbers of exposed persons were too small and too heavily weighted towards young adults to provide good data on age effects. Adult Japanese fishermen, although few in number, and Marshall Islanders [C6] seem not to have exhibited an excess risk. Non-haematopoietic tumours do not appear to have arisen in these groups in detectably higher frequencies.

441. For adults exposed to chronic doses of radiation either occupationally or through the ingestion of radioisotopes for therapeutic purposes or as a result of nuclear testing, the duration of exposure is too long and, typically, the dose too low to provide useful information about special effects of age at exposure.

C. GENETIC CONSTITUTION

442. Given the genetic variability that exists between individuals within a group and between groups, it is
reasonable to presume that the risk of cancer may vary among individuals of the same sex, age and apparent life-styles when exposed to the same amount of ionizing radiation. A number of relatively rare, largely recessive disorders are known in which fibroblasts from trait-bearers are deficient in the repair of some radiation damage in vitro; it is also known that these individuals are at increased risk of a variety of malignancies, especially malignant lymphoma and leukaemia [K11]. Cell lines from patients with one such disorder, xeroderma pigmentosum, in which UV light is a mutagen, did not disclose a cross-sensitivity in regard to cell-killing with gamma radiation, but enhanced sensitivity to cell-killing has been reported in vivo in irradiated children. Some cell lines from patients with heritable diseases, including cancer-prone ones, have shown cell-killing sensitivity after such radiation [A7, G5, P10, P11], but this is not always found [W10]. One study [F7] has reported that cell cultures manifesting a variety of chromosomal aberrations have shown similar low-dose response estimates.

443. The carriers of one major disease, ataxia telangiectasia (AT), may have been subjected to irradiation in numbers sufficient, eventually, to show an excess of cancers, if it exists. The gene for AT is relatively common in Israel, where it is expected that at least some children irradiated for tinea capitis would be carriers of the gene. The latest report [R22] suggests that Moroccan children, who have a high frequency of AT carrier status, are especially susceptible, among the total Israeli tinea capitis study series. This study did not report thyroid cases. However, in another report from the Israeli series, the thyroid cancer pattern may also reflect this fact, although genotyping has not been done on the cohort and only some of the children were given ionizing radiation as opposed to UV therapy.

444. The cells of these individuals carry two copies of the "susceptibility" allele, on each parental chromosome, i.e., they are homozygous for an abnormal allele (form of the gene). However, in their families there will be many heterozygous individuals whose cells have only one copy of the abnormal gene, the other being normal. Indeed, not only in these families but also, by virtue of the frequency of the susceptibility allele, in the larger population, there will be a substantial number of individuals, perhaps several per cent, who are heterozygous "carriers" of the abnormal allele. For them, affected relatives will be unlikely and would arise only when a heterozygote and another carrier marry, a relatively rare occurrence. Substantial speculation has centered on the likely cancer risks of individuals heterozygous for these genes. Little direct information exists as yet since there is no simple, easy test for heterozygotes. However, on the presumption that the parents of affected individuals must be carriers (except for very rare instances in which a mutation occurred in the child), some testing of the radiosensitivity of fibroblast cultures from these parents has been carried out. This work, though still tentative in nature, suggests that there is an intermediate level of radiosensitivity, measured by cell survival, between affected and normal homozygotes [P10]. While it is unlikely that excluding very small subsets of abnormally radiosensitive individuals would alter population risks importantly, their existence will require separate estimation.

445. The Li-Fraumeni syndrome is a dominantly inherited genetic susceptibility to cancers of many organ sites [L13]. Normal fibroblasts from Li-Fraumeni family members are resistant to killing by radiation; Chang et al. [C18] found that in non-irradiated cultures of such cells, the c-myc oncogene has a threefold to 18-fold increased expression and that c-raf-I expression was also elevated. Kasid et al. [K23] have found that elevated expression of the c-rf-I oncogene is associated with a cell line of laryngeal carcinoma which is radioresistant (in vivo and in culture). Why this oncogene should apparently be associated with carcinoma risk and radioresistance is not clear.

446. In retinoblastoma when the individual is an obligate heterozygote for a cancer-related region on chromosome 13, the subsequent risk of radiogenic tumour is a reflection of the susceptible genotype.

447. Less has been written, indeed less is known, about the role of genetic predisposition to specific malignancies and the relationship, if any, of this predisposition to radiation-induced risk. Are, for example, women who come from "breast-cancer families" more prone to develop breast cancer after irradiation of the breasts than women who do not come from such families? One study in Japan may begin to provide an answer [Y3]: there was an increased risk of second tumours in women with a family history of breast cancer relative to those without such a history, and there was evidence suggestive of an interaction with radiation in producing this risk. A substantial fraction of colon cancer cases is familial, although to date no study has looked for an excess susceptibility in irradiated persons from high-risk families. A variety of shared environmental factors could lead to a familial appearance of cancer, so that a definitive answer to the question of carrier susceptibility must await the development of practical tests for genetic susceptibility.

448. As reviewed in detail above, many second tumours following radiotherapy occur in individuals whose primary tumour was of a heritable kind. In some of these families there is an excess of cancers of other types in the relatives of the probands. Such relatives do not suffer the index disease, but they may be carriers of some modifier allele at a different genetic locus or, for some other reason, predisposed to develop cancer. Retinoblastoma and childhood sarcomas have both been involved in such studies. If these probands are from cancer-susceptible families, or if their cancer reflects a cancer-proneness, dose-response estimates for them may be of little value to the population as a whole, but the identification and characterization of susceptible genotypes may be extremely important in their own right.

449. Data relevant to these issues are sparse, but those that are available suggest there may be a small
but non-trivial fraction of the human population that is prone to develop cancer and, as a consequence, may be much more liable to develop radiation-related cancers. This may mean that the average dose-response pattern is a relatively poor indicator of individual risk. It may be too low for those individuals especially predisposed, and too high for those individuals who are not at special risk. However, to improve the estimation of risk, one must be able to identify the susceptible individuals, which is not practicable at present.

450. In ankylosing spondylitis patients there is strong association with specific genes at the histocompatibility loci, in particular an allele known as B27. Individuals with at least one copy of this allele are much more susceptible to spondylitis than are those with other alleles. It is thought that this may involve the development of auto-antibodies in such individuals after exposure to some agent, possibly an unidentified virus. At present there is no evidence that the HLA type is related to cancer or to cancer induction, so that from this point of view the ankylosing spondylitis patients may be thought of as representative of the general population.

D. ETHNIC CHARACTERISTICS

451. Shore et al. [S16, S27] have suggested that radiation-induced skin cancer is functionally related to the degree of pigmentation of the exposed individual. No increase in skin cancer with exposure has been seen among the 2,226 blacks who made up 25% of their tinea capitis population, but 41 cases occurred in the white children who made up the remaining 75%. Nor has an increase been seen among the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki [C4, O2]. These results correspond to the prevailing skin cancer rates in blacks and in Japanese. This suggests that partially transformed cells, exposed to the DNA damage of UV radiation in light-skinned individuals, may become fully transformed. However, no UV-radiation cross reaction has been found in cell lines carrying UV-sensitive genotypes (reviewed above).

E. HORMONAL EFFECTS

452. A deficit in breast cancer has been observed in the cohorts of women who had been treated for gynaecologic disorders (malignant and non-malignant) [B12, L11, W6]. At the same time, ovarian cancer was seen to be reduced in women who had been treated for gynaecologic cancer [B12]. These observations agree with a cell-killing effect at the ovary, depriving the breast of oestrogenic compounds that may contribute to carcinogenesis in partially transformed breast cells. However, breast cancer was also reduced in women treated for benign conditions, who did experience elevated ovarian cancer [W6], the explanation is therefore not obvious at present, and non-representative subjects (i.e., subjects who present an inappropriate expected risk) may be responsible.

453. A study specifically designed to detect interaction between various hormone-related variables and breast cancer risk in women irradiated for postpartum mastitis was conducted in 571 patients and 993 controls in Rochester, New York, United States [S37]. This study found that women with benign cystic breast disease were at excess risk following radiation, but because the benign disease occurred after irradiation, a causal relationship could not be established. Oral contraceptive use, family history of breast cancer, late age of parity, menopausal hormone use and ovarian-related factors (e.g., missed menstrual cycles) were tested, but no interactive relationship with radiation was detected. Another United States study reported similar results [B1].

454. In the Japanese data [T14], breast cancer risk seems to be less if the radiation exposure occurred after menopause. However, this may be a cohort effect, attributable to different levels of hormonal stimulation in the United States and Europe on the one hand, and Japan on the other. Japanese-American women are developing age-specific breast cancer frequencies much like those of other Americans, and breast cancer is becoming more frequent at older ages in Japan. If this is a cohort effect, and if radiogenic breast cancer is related to the hormonal stimulation that appears to be responsible for these international differences, post-menopausal radiogenic breast cancer may increase in Japan [T14].

455. Tokunaga et al. found a slight but non-significant excess risk among women who had borne their first child after age 30 [T14]. Nulliparous women may also have elevated radiogenic risk [B1]. Similarly, irradiation after the first childbirth seemed to lead to elevated risk; age at first childbirth is certainly related to the occurrence of breast cancer, but how this interacts with radiation is not known. This and other studies seem to suggest an age effect on breast tissue susceptibility.

F. OTHER DISEASES

456. It has already been discussed whether individuals irradiated for the treatment of cancer suitably represent the general population in terms of their susceptibility to radiation-induced cancers. In general, most studies find similar patterns of radiation risk. An exception to this is excess sensitivity among children who have genetic predispositions, which suggests that children exposed for cancer treatment should not be considered for general risk estimates. Presumably some adults also have greater genetic susceptibilities for cancers, but these individuals cannot be identified in general populations.

457. Although the non-random HLA genotypes in ankylosing spondylitis patients (reviewed above) may not affect their radiation susceptibility, they clearly suffer from proportionally different causes of death than the general British population [S28]. Their pattern of relative risk for a variety of causes is given in Table 1 of [S28]. In addition to the colorectal cancer which may be confounded by the higher risks
of colitis and its associated cancer risks in these patients. Many other causes of mortality are different from a general population. Even if this does not apply to their general cancer susceptibility, it clearly affects the interpretation of relative risks derived from the United Kingdom baseline cancer and general mortality rates.

V. ENVIRONMENTAL FACTORS THAT MODIFY RISK

458. It has been asserted, based on world-wide cancer data, that 85-90% or even more of all cancers are avoidable; that is, that they are due to exposures to environmental carcinogens, e.g., smoking, diet, personal habits and the like [D13]. This assertion is based on the observation that age-standardized incidence rates for virtually every type of cancer vary greatly among the populations of the world. Doll and Peto, in their review of cancer patterns in the United States, have estimated that 1-1.5% of all cases in that country are radiation-induced (non-occupational sources of radiation) [D13]; some of these cases will be due to natural background radiation, but the remainder will be due to man-made sources of exposure.

459. The most systematic data on variation in site-specific cancer incidence, by age and sex, is the series of volumes published by the International Agency for Research on Cancer (IARC) [W17]. They provide the best available baseline cancer risks and, while they include the effects of radiation on a population basis and cannot be used specifically to identify environmental causes, they can be used in computations of risk assessment, as discussed in chapter II. Radiogenic effects will be functions of the baseline risk. In addition, as seen in chapter III in regard to second cancers in patients irradiated to treat cancer, radiation risk is highly dependent on the effects of other risk factors.

460. The observed pattern of world-wide cancer variation is not highly correlated with ethnicity in any simple way that would suggest that this variation has a genetic basis, so it is generally assumed that environmental factors must be responsible. It is usually also assumed that in any population a large fraction of the baseline cancer rate, for any tumour site, is determined by local exposures to various agents (including radiation). Smoking and diet, pollutants in the environment, endogenous as well as exogenous hormones, and many other agents are known to be associated with variations in cancer risk.

461. Among the more elusive of the host factors and environmental factors that can influence the occurrence of a radiogenic cancer are the health status and lifestyle of the exposed individual. Their roles have been difficult to assess, for the variables themselves are difficult to define and to measure adequately. Smoking habits are more than just the sum of the cigarettes one smokes daily, weekly, annually or in a lifetime of smoking; moreover, these habits change with age and perception of risk. Data are beginning to be available that are relevant to three questions, namely: (a) what roles do smoking, diet, and the like play in cancer risk? (b) are life-style attributes related in any way to the absolute or relative risk differences in the irradiated? (c) can an understanding of the interaction of risks lead to an understanding of the action of radiation?

462. Regardless of the answers to these questions, relative and absolute excesses of cancer attributable to radiation must at present be evaluated in the context of local baseline patterns. For the cohorts of individuals who have been exposed to large doses of radiation, the levels of environmental risk exposure have been changing in the populations in which they live. Without adequate cognizance of these changes, it will be difficult to identify the effects of radiation, per se, or to say whether the effects of radiation are the same in populations with vastly different socioeconomic environments.

463. In addition to changes in mean levels of exposure within a population over time, there will be inter-individual differences in exposure that are relevant both to the analysis of specific cohorts and to the estimation of future risk. Although the data are limited, in many study cohorts it has been possible to make observations, or plausible inferences, about the role of certain environmental co-variates. These will now be reviewed.

A. SMOKING

464. Clearly, cigarette smoking is one of the most definite, and easily assessed, risk variables; it applies to cancer of the lung in smokers whose lungs are exposed to radiation, as well as to certain other tumours. However, Kato and Schull [K7] found no evidence that smoking increased the radiation-induced lung cancer incidence in Hiroshima and Nagasaki disproportionately. Prentice et al. [P7] and Kopecky et al. [K22], in a more elegant and broader analysis of the same data, reached a similar conclusion. Persons heavily exposed to both cigarette smoke and radiation had significantly lower cancer mortality for all cancers except leukaemia, stomach cancer and digestive cancer other than stomach cancer than predicted with a multiplicative risk model. The lung cancer relative risk function could not be distinguished as either a multiplicative or an additive form, though there might have been a slight preference for the latter.

465. Women treated for gynaecological disorders have experienced an increase in the incidence of cancer at smoking-related sites, including lung, bladder, oropharynx, and oesophagus [B2, B12, W6]. This has been observed in irradiated and non-irradiated patients. Since smoking is a well-established risk factor for cancer of the cervix, which typically selects for women of lower socio-economic status, some of the excess risk of smoking-related cancers in these women may be due to their smoking habits; alternatively, it may be that they were susceptible to cervical carcinogenesis for a variety of reasons; among them, smoking. They may have been more susceptible to smoke than the
population from which their expected rates were computed [B12, W6]. In a case-control analysis of a subset of the cervical cancer series, Boice et al. [B38] were able to show an association between smoking and smoking-related cancers, as well as for other known risk factors and their associated cancers (i.e., nulliparity effects on breast cancer risk, and obesity and menopausal oestrogen therapy for endometrial cancer).

466. The relative risk of lung cancer in the international cervical cancer study of women under age 40 was more than 12, a much greater risk than can be accounted for by the effects of smoking in the patients [B12]. For women who had not received irradiation, the relative risk was the highest of any group in the study, about 3, and a similar excess of bladder cancer was found in the women treated for benign conditions [B12, W6]. A different series, of 2,500 French women treated for cervical cancer, observed 10 cases of bronchial carcinoma, with only 28 months, on average, intervening between the diagnoses [S36]. This latency time is too short for radiation to have induced cancer in the lungs. It is possible that the excess lung cancer, at least, reflects the misclassification of metastatic cervical cancer has also been considered [B12, D9, S36], although these authors argue that the persistence of excess risk in the large international study after 20 years suggests some of the excess may be real. Given the low dose of radiation received by the lung, a truly radiogenic effect would be difficult to detect [B12].

467. One extensively studied potential interaction is that between smoking and radiation in occupationally exposed underground miners. The alpha radiation of the radon daughters present in the air of underground mines provides long-term, generally low-level exposure to the lungs, as does smoking. Some aspects of these studies have been mentioned earlier.

468. Most of the miner populations studied had a high percentage of smokers, so that the independence of the two effects has been difficult to evaluate accurately. However, Navajo Amerindian men working in mines in New Mexico, United States, also developed excess lung cancer and relatively few of them were smokers [S20]. None the less, the data on smoking and radiation with respect to miners are complex and inconsistent [C4]. One study of iron miners in northern Sweden indicated that smoking had, roughly, an additive effect in the exposed miners [R7], while another [D12] purported to find an interactive effect. In their recent study of six Czechoslovakian mining groups, Seve et al. [S51] found smoking to have an additive effect. Thomas et al. [T20] have found an effect intermediate between additive and multiplicative. However, in an analysis of data from uranium miners in the Colorado plateau (an area including parts of the states of Colorado, Utah, New Mexico and Arizona, United States), Whittemore and McMillan [W12] found strong support for an interactive relationship between smoking and radiation exposure. It should be noted that the dose estimates were uncertain and may have been higher than in other series. This could explain some of the difference in results [C4]. Also, while earlier analyses of these data had not revealed an interactive effect [C4], the more recent study used proportional hazards analysis, a better method than categorical analysis because it compares risk within the exposed cohort and is not dependent on assumptions about control group risks. Whittemore and McMillan also demonstrated that the models fit the data better when cumulative exposure (to both smoking and radiation) was used, instead of average annual exposure. The best data on this topic show that the interaction between smoking and radon daughter exposure is intermediate between additive and multiplicative [S51]. This was also the conclusion of the BEIR IV Committee [C20].

469. There is clearly a radiogenic risk of lung cancer in the absence of smoking as a co-factor. In general, the dose between the absolute risk for miners who smoke and that for those who do not has been small, but the difference in the relative risk between the two groups is great [C4, R7]. As was true in some mining studies [C4, R7], data from the Japanese atomic bomb survivors fit additive and multiplicative models almost equally well [P7, K22].

470. The time from first exposure to lung cancer has commonly been about the same for smokers and non-smokers [C4, R7], implying that radiation, and not smoking, was responsible. Even in the Colorado miners, where an interaction was inferred, there was no evidence for an age of onset difference [W12]. This finding disagreed with earlier analyses of these data [W13], which seemed to show such a difference perhaps due to overestimation of the exposures [C4, R7, W12]. The latency period reported for Japanese non-smokers is longer than that for smokers. Although some of this difference could also be due to errors in the estimation of smoking and radiation exposures, some of it may reflect the dissimilarity between chronic mining exposures and the single exposures in Japan. There have been large differences in the exposure levels of the various mining cohorts, and dissimilar doses can have disparate effects (interactions not apparent in some situations may be detectable in others).

B. DIET

471. Stomach cancer is very common in Japan, and some dietary factors have been implicated (e.g., the high-temperature cooking of meat and fish and preservation methods for fish). Thus, radiation exposures in Japanese can be expected to have effects that are related to the high level of exposure to these other risk factors. In a multiple regression analysis of stomach cancer in Hiroshima and Nagasaki, Ikeda et al. examined the relative importance of various risk factors for stomach cancer [I8]. Their study, which had a total residual (unexplained) variance of less than 1%, showed a statistically significant association between stomach cancer risk and age, sex, consumption of milk and consumption of broiled (but not dried or pickled) fish. Radiation dose had a much smaller, non-significant effect [I8].
472. Stomach cancer in irradiated persons in Hiroshima and Nagasaki tends to occur more often in areas of intestinal metaplasia, and the frequency of the latter appears linearly related to dose [M15]. As noted earlier, intestinal metaplasia in the lower third of the stomach is a characteristic precursor of gastric carcinoma in Japan, suggesting that irradiation has interacted with predisposing dietary factors. Because gastric cancer rates are dropping in Japan as diet changes, it is imaginable that Japanese exposed to radiation at a future time would have fewer partially transformed cells and, hence, a lower risk of radiogenic cancer. Radiation may induce cancer by increasing the prevalence of the precursor state as well as by further transforming cells already in such a state.

C. INTERACTION BETWEEN THERAPEUTIC MODALITIES

473. The findings in patients given combined radiation and chemotherapy for cancers, especially adult cancers, were described earlier. Generally, the strongest effects were those of chemotherapy, and some studies found no specific radiogenic effect on solid tumours or on acute non-lymphocytic leukaemia (ANL), only a chemotherapeutic effect. Some applications of radiation have probably led to intense local irradiation and cell sterilization, which may actually weaken the combined effect of the two types of therapy. It is not known if either the presence of disease or the method of applying the therapies affects the nature of any interaction. As reviewed above, in several adult cancer series, the relative risk of persons who had not received radiotherapy was greater than 1.0, which shows how important it is to have proper reference groups when comparing the effects of different modalities of therapy. Even if those treated with combined therapy show greater cancer risks, if the patients do not represent the population at large, the inferences about the effects of therapy, including radiation, will not be precisely applicable to a general population of exposed individuals. In any case, chemotherapy is commonly part of the treatment in which radiotherapy is used, so that the potential effects of the latter alone cannot be readily assessed; this is particularly so in view of the constantly changing therapeutic schedules and agents.

474. One of the most interesting sets of subjects in which to examine the effects of combined radiation and chemotherapy is the set made up of patients who were treated for retinoblastoma, as noted earlier, about 25% of patients with this childhood tumour have a genetic susceptibility to it and to other cancers also, this cohort provides an opportunity to examine the effects of the different therapies both inside and outside a well-delimited radiation field. For patients receiving no chemotherapy, there are good baseline data.

475. An analysis of British retinoblastoma patients has been reported by Draper [D15] (Table 43). The small sample sizes and the fact that most patients given chemotherapy were genetic cases limited the analysis to those with the genetic form of the disease.

The risk of a subsequent cancer among patients receiving both kinds of therapy was greater than for those receiving only one kind, both at 12 years and (especially) at 18 years after initial diagnosis. These differences were significant at the 5% level, although Draper noted that since the modes of radiotherapy may have been different for those also given chemotherapy, there could not be too much emphasis on the specific numbers. Thus, in genetically susceptible individuals, combined therapy adds to the risk of cancer: the excess risk is apparently experienced both inside and outside the radiation field. The fact that the effect of combined therapy seemed much greater after 18 than after 12 years suggests that an even greater effect may be revealed as more follow-up time accumulates.

476. In the data on Wilms' tumour [L3], combined chemo- and radiotherapy was given to four of the nine radiation-associated second tumour patients. Combined therapy did not increase the risk of cancer relative to radiation therapy alone, when all cancers were considered. The relative risk of chemotherapy, among irradiated patients, was 1.02. However, if only tumours arising in the field of irradiation were considered, the relative risk of chemotherapy was 1.50, significant at the 5% level. These patients received orthovoltage therapy.

D. STATISTICAL REFLECTION OF HIGH POPULATION RISKS

477. In the parallel analysis of cancer data from ankylosing spondylitics and the Japanese series, Darby et al. [D11] plotted both the relative risk and the excess risk of various cancers against the expected risk in the two populations. These are shown in Figure XIII. Most of the tumours cluster in a small area on such a graph (RR < 5: risk per 10³ and year < 25). The points for stomach cancer, which is very prevalent in Japan, and for lung cancer, which is very prevalent in the United Kingdom, are among the few outliers on the respective graphs. Both exhibit very low relative risk contrasted to their population risks. It appears that the pattern observed by Darby et al. is, with the exceptions of leukaemia and CNS tumours, a linear one, with the relative risk roughly between 1.5 and 3 for all epithelial sites.

478. Central nervous system (spinal cord and nerve) tumours were much elevated, relative to their normally rare occurrence. This is probably because these tissues are seldom exposed to environmental mutagens (blood-CNS barrier), with almost no mix of spontaneous and radiogenic tumours in the data sets. For leukaemias, the relative risks were different in the two groups (about 3 in spondylitics and 9 in the Japanese survivors), but the population prevalences were similar. The relative risks for both sites (CNS and leukaemia) were different from the relative risks for most carcinomas. The explanation for this is not clear, but the discrepancy highlights the difference between haematopoietic and epithelial tissues and perhaps serves as indirect evidence for the importance of environmental risk factors in the epidemiology of radiogenic carcinomas.
E. GENERAL CONSIDERATIONS ABOUT INTERACTIONS

479. The many factors discussed in the previous sections indicate that there are numerous ways in which radiation could have, or could appear to have, an effect on the irradiated individual. Clearly, it is very important to ensure that the expected rates with which the risk in irradiated subjects are compared are representative of their population. The 1980 BEIR III Report [C4] attempted to derive summary risk coefficients of the excess cancers to be expected per 10^6 PYGy.

480. The BEIR III estimates [C4] were developed by considering all the data available, in an effort to synthesize the information from a variety of heterogeneous data sets. There are, however, pitfalls in such an approach. One reflection of the uncertainties surrounding the use of these estimates shows up in a comparison contained in one of the reports by the international group studying the risk of second cancer in cervical cancer patients [B12, D9]. This comparison showed a poor correspondence between the number of excess cancers (based on the expected number of cases in the referent populations of the eight collaborating tumour registries) and the number of excess cancers that was predicted by applying the BEIR III risk estimates [C4] to the doses and exposure times in the cervical cancer data. The comparison is given in Table 44. It should be remembered that the expected cases were based on risk coefficients per 10^6 PYGy derived largely from the Japanese T65 dose estimates, and the comparison in Table 44 is based on the cervical cancer data in [B12].

481. The biggest difference is in the leukaemias; the authors attribute this difference to cell sterilization in the pelvis and hence to an overestimate of the effective dose [B12], and which their case-control study, taking marrow-weighted doses and cell-sterilization into account, showed to be an artefact of assuming uniform dose to all marrow (i.e., when marrow-weighting is done, the discrepancy largely disappears [B36]. Dose-fractionation may also have reduced the apparent relative risk per unit dose relative to that found in other studies [B36]. However, the difference is too large to be attributed solely to that factor. In addition, more excesses of lung cancer have been observed than were predicted and fewer excesses of most other cancers, notably breast, kidney and bladder. These have plausible explanations which were reviewed earlier (paragraphs 269-284). In general, however, it must be emphasized that (a) cancer patients are not representative of the population at large in respect of many risk-factor exposures; (b) risk-factor exposures may be relevant to more than one type of cancer; and (c) radiation itself may have direct or indirect effects on the risk of cancer in other organs. Thus, to understand the true risk associated with radiation may be difficult, since good background cancer risks are not usually available for the special subset of individuals exposed to ionizing radiation.

482. These facts stress the importance of taking other environmental and host factors into account. They also show that whole-population exposures may in many ways be more informative than exposures of selected population subsets, and that internal controls, rather than the whole population, may be the most appropriate comparison group. In the instance of the cervical cancer data, the appropriate comparison group is probably the benign gynaecologic disease group (to the extent that they in fact did not receive radiation therapy themselves). The data from Hiroshima and Nagasaki are as close to the ideal in this regard as any available.

VI. SUMMARY OF RISK ESTIMATES IN MAJOR COHORTS

A. STUDIES PROVIDING SUMMARY RISK ESTIMATES

483. This chapter provides overall summaries of radiogenic cancer effects from the most comprehensive data sources currently available. Details from studies of tissue-specific exposures or susceptibilities were reviewed in chapter III. Here, results relevant to risk estimation and projection are given.

484. There are only three sets of data from which radiation effects can be estimated for a large variety of sites: those for the Japanese atomic bomb survivors, the ankylosing spondylitis patients and the cervical cancer patients. In all three, the sample was large, the individuals were followed for long time periods and an essentially similar kind of exposure was received by many parts of the body. Each set of data has its own characteristics. The Japanese data included internal controls, as did the cervical cancer data (i.e., patients treated without radiation). All the data are for short-term, low-LET exposures. In the spondylitics and the cervical cancer patients, groups of tissues receiving approximately the same level of dose were analysed jointly; the whole-body exposures experienced in Japan could not, of course, be included in this analysis. Only from Japan do we have effective comparisons of the exposure effects in males and females. The Japanese cohorts also provide the most comprehensive data from which to estimate dose-response patterns.

485. The most commonly used measure of the effect of exposure on a given site is the number of excess cancer cases per 10,000 persons exposed to 1 Gy after one year (10^9 PYGy), although some estimates count experience only after a five-year or 10-year latency period. The methods by which this number has been computed were discussed in chapter II.

486. Summary estimates of site-specific risk coefficients are available for the Life Span Study in Japan [K7], the Nagasaki tumour registry [W5], the ankylosing spondylitis patients [S31], the BEIR III Report [C4] and an older report from the ICRP [19]. Land [L1] has collated some additional data. These risk estimates can now be revised in the light of newer dose estimates and longer follow-up times. In this chapter, the latest reports available are summarized.
B. PROJECTION OF RELATIVE RISK IN THE MAJOR STUDIES

1. Results from exposure to treat cervical cancer

487. For most sites, the international study of cervical cancer patients [B12, D9] found that the number of excess cancer cases was smaller, except for the lung, than would have been predicted based on: (a) the number of person-years at risk; (b) the expected number of cases in the appropriate registry populations; and (c) the BEIR Committee estimates [C4] of the excess number per 10^4 PYGy for the same sites. This difference has already been set forth in Table 44, at which point the question was raised of how well the irradiated subjects typified their larger populations.

488. Pooled heavily irradiated sites. To summarize the general effects of heavy irradiation such as was received to treat cervical cancer, the authors have analysed the joint manifestation of second primary cancers occurring in heavily irradiated sites; that is, sites close to the irradiation and likely to have received more than 1 Gy (stomach, small and large intestine, liver, gallbladder, pancreas, uterine corpus, ovary, other genital organs, kidney, bladder, bone and connective tissue). These will be referred to as heavily irradiated sites. In general, the pattern observed agrees with what has been found in Japan and in the ankylosing spondylitics [D11]. The details of the separate registries and site-by-site analysis may be found in [D9]; the results are summarized in [B12], from which the following is taken.

489. The minimum latency period for the heavily irradiated sites after cervical cancer was about 10 years; the excess risk thereafter did not diminish for at least 30 years. Figure XV compares these exposed patients

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**Figure XV.** Risk of a second primary cancer occurring in or near the pelvis (close and intermediate sites), related to time of diagnosis of cervical cancer, for patients treated with and without radiation. The number of cancers are given above the 80% confidence bars.

**Figure XVI.** Relative and absolute risks for second primary cancers occurring in or near the radiation field (close and intermediate sites), related to age at exposure, exclusive of the first 10 years of observation, for women treated with radiation. The number of cancers are given above the 80% confidence intervals.

[B12]
Figure XVII. Relative risks of second cancers in women irradiated to treat cervical cancer.

[B12]
with non-exposed cervical cancer patients, who manifested no increased risk when all the heavily irradiated sites were aggregated. Many of these women were followed for the rest of their lives (some lived into their nineties) and it was seen that risk apparently continues to remain elevated during all post-irradiation life [B12].

490. In terms of relative risk, women are more sensitive if irradiated under the age of 30, but thereafter, age at irradiation appears to have little effect for these pooled sites. Since the background risk of cancer at these heavily irradiated sites increases with age, the absolute risk rises with age at exposure. This is shown in Figure XVI. The Japanese data have typically showed high sensitivity among those who were young at the time of the bombings.

491. Individual heavily irradiated sites. These same data have been analysed separately for each site [B12, D9]. Some of these findings are important enough to warrant review here. The patterns of relative risk following exposure at some of these sites are given in Figure XVII. Table 26 gives the most recent relative risk values for these projection effects, pooling data on all ages at exposure, based on a subset of the cervical cancer patients and a control group for comparison.

492. Figure XVII shows that bladder cancer increased gradually with time, with a relative risk of about 3.0. The projection effect appears to be radiogenic. As noted earlier, however, bladder cancer was among the smoking-related sites with similar patterns in the non-irradiated; but in the non-irradiated it decreased with time. While it is curious that rectal, but not colon, cancer was elevated, the projection pattern of rectal cancer is clearly the kind of pattern to be expected for radiation-related malignancies, and it obtained only among irradiated patients [B12]. Endometrial cancer (corpus uteri) had a relative risk of less than 1.0; this may be due, at least in part, to a high prevalence of hysterectomy. The increase in the relative risk 10 years after irradiation, with a levelling off afterwards, suggests a radiation effect. The marked and significant increase in “other genital cancers” refers mainly to an increase at the vulva, vagina, and unspecified sites; these sites probably share risk factors (e.g., HPV susceptibility) and may not reflect a radiogenic effect; they were at elevated risk in all groups in the study.

493. The bladder cancer projection is typical of a radiogenic epithelial cancer, except that it appeared in the first 10 years after irradiation. Boice et al. [B12] attributed this to mis-classified cervical metastases. After a 15-year latent period, there was no association between risk and age at exposure. The high level of risk and the increase over time suggest that more than the confounding effects of smoking are involved [B12].

494. In terms of sites remote from the source of exposure, an increase in smoking-related cancers was found, most dramatically in the lung. The incidence pattern (relative risk highest five to 10 years after irradiation and no excess cases after 20 years) is not typical of radiogenic lung cancer. The deficit of breast cancer is attributed to ovarian ablation by the radiation, which indirectly has a protective effect.

495. Haematopoietic tissue. Figure XVII shows the overall pattern of relative risk of leukaemias following irradiation. Pelvic marrow in these women received 3-15 Gy. While there was a marked deficit in leukaemias, relative to the BEIR III estimates (see Table 44), the pattern of excess leukaemias matches the pattern, with regard to projection effects, that is expected for radiogenic leukaemias (an excess beginning two to five years after exposure and diminishing after about 20 years). The relative deficit in excess cases is attributed to local cell killing [B36]; the dose received by the peripheral marrow is estimated to have been <1 Gy, a dose which is leukaemogenic. The figure also shows the small excess of multiple myeloma and its persistent increase.

2. Results from exposure to treat ankylosing spondylitis

496. Results have recently become available that summarize some of the effects seen in the patients exposed to treat ankylosing spondylitis. The analysis presented here pertains only to the effects of single courses of x-ray treatment [D21, S28, S31]. The expected numbers were derived from British national mortality statistics. Table 45 presents the relative risks for major groups of sites as a function of time since irradiation [D21]. In these data the relative risk for leukaemia can be seen to rise rapidly and to persist beyond 25 years after exposure. The relative risks for the other sites remained approximately constant for the first 25 years after exposure, with values between 1.5 and 2.5, but then tended to disappear. Little effect, overall, was seen in lightly irradiated sites.

497. The site-specific projection effects are given in more detail in Table 46, also from [D21]. The authors found that for several sites the relative risk was elevated as early as up to two years after exposure as well as from three to nine years after exposure. They attributed this unexpectedly early appearance of excess relative risk to the possibility that tumours that had existed had been mistaken for ankylosing spondylitis, and they suggested that the relative risk at six to eight years' post-exposure was only slightly different from 1.0 [S31]. In their view, these data are consistent with the Japanese and other results for solid adult tumours in terms of the first appearance of excess risk, though not in terms of the disappearance of excess risk after 25 years.

498. Table 47 gives the relative risk values for the same series of patients as a function of their age at exposure, for leukaemia and for the heavily irradiated sites. The relative risk for leukaemia appeared to be slightly lower among those exposed at under age 25 and roughly constant afterwards, but none of the differences were significant. Also, the differences were not significant for all heavily irradiated sites combined.

499. A recent study has improved the dose estimates for the spondylitis patients [L16]. Earlier estimates, in
particular the BEIR III estimates, were very different from these new values, so that summary tables of the new values are included here for reference (Tables 48 and 49). This study was based on a sample of 934 patients (1/15 of the total series), for 903 of whom organ dose estimates are reported in the tables. Estimates were based on an Oak Ridge Laboratory program [W19] that models the process based on a mathematically defined human phantom. It is clear from the tables that there was great inter-individual variation in dose; thus, dose-response patterns from the entire series of over 14,000 patients are not based on precise individual exposure estimates. The new dose estimates are about 19% higher than prior estimates and very different from BEIR III [C4], although they are close to recent estimates by Drexler and Williams [D22].

3. Joint analysis of Japanese (T65D) and ankylosing spondylitis data

500. The detailed analyses of the risk effects from Hiroshima and Nagasaki, based on the revised (DS86) dose estimates, constitute the most important single data set on risk effects in existence. However, to augment the information from this and the large series of ankylosing spondylitis patients, Darby et al. [D11] analysed the Japanese and spondylitis data jointly. A summary of their results and of some of the basic data are presented. However, it should be noted that (a) the data from Japan apply to the old dosimetry (T65DR); (b) the spondylitis doses have been revised [L16]; and (c) the spondylitis risks have been revised [D21] since this joint analysis was prepared. Therefore, the joint analysis must be considered only rough and qualitative in nature, and it is to be read carefully in regard to carcinoma risks more than 25 years after exposure.

501. With these cautions in mind, Table 40 gives joint, summary relative and absolute risk values for the Life Span Study [W5] and the spondylitis patients [S28]. This paper [D11] provided some summary statistics on projection effects, with regard to a series of selected sites for which results between the two data sets could be meaningfully compared.

502. In the spondylitis, absolute risk standardized for time since exposure increased rapidly with age at exposure; in the Life Span Study, there was less evidence of such a trend. The result was similar for absolute risk by time since exposure standardized for age at exposure: a trend in the spondylitis but not in the Japanese. For the studies to be compared more directly, the observed Japanese risks were standardized to the same exposure-time distributions seen in the spondylitis, and this produced clear trends in the data from Japan for age at exposure and time since exposure. The joint estimate was an absolute risk of 31.7 per 10^5 PY (SE = 8.5) for every 10-year increase in age at exposure, and the studies did not differ significantly. In Japan, but not in the spondylitis, there was a statistically significant (p < 0.05) trend in time since exposure. The combined analysis showed no significant difference (p > 0.10), and the joint estimate was an average increase in absolute risk with time since exposure of 34.0 per 10^5 PY (SE = 15.7) for each six-year time period. This was significant at the 5% level.

503. Relative risk results are summarized in Figure XVIII, which shows that in the ankylosing spondylitis

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**Figure XVIII.** Relative risk of cancer in selected sites combined in relation to age at exposure and time since exposure for the ankylosing spondylitis series and for the Life Span Study sample (T65DR doses).

[D11]
patients there were no trends in relative risk for age at exposure, and only before 10 and after 22 years did relative risk fall below its generally flat projection pattern; there was no evidence that these two factors interacted [D11]. The data from Hiroshima and Nagasaki showed significant linear and quadratic trends in relative risk with age at exposure (declining with increasing age), and a log-linear trend in relative risk could be fitted to the data. The trend in relative risk with time since exposure was roughly level, both before and after incorporating a log-linear trend in relative risk with age at exposure. In analysing these jointly, Darby et al. found no trend in the relative risk in time since exposure; for five to 30 years after exposure, the relative risk remained about constant. Jointly there was a significant log-linear trend in relative risk for age at exposure, with the joint estimate of the trend in log (RR) with exposure age of \(-0.5\) (SE = 0.13).

4. Recent results from studies of the Japanese exposed to the atomic bombings

504. The Atomic Bomb Casualty Commission and its successor, the Radiation Effects Research Foundation, have at various times used a variety of measures of individual exposures to the atomic bombings of Hiroshima and Nagasaki. These included distance from the hypocentre [M38]; the presence or absence of the symptoms associated with acute radiation illness [N10]; and, now, no fewer than three separate physical dosimetrys, namely, the T57 [R19, A17], (for an application of these doses, see [110]), the T65 [M24], and the new Dosimetry System 1986, or DS86 [M39, N11, R20]. Each successive method of expressing doses has necessitated a re-estimation of the risk coefficients associated with the various known effects of ionizing radiation and a re-examination of the dose-response relationships. With these changes there has emerged a better ability to estimate the risk coefficients in terms of organ absorbed doses or organ dose equivalents rather than in terms of kerma, whether free-in-air or in-house (shielded).

505. The newest system of dosimetry is an outgrowth of a series of events. In 1975, Prege of the Los Alamos National Laboratory (United States) re-examined the gamma-ray and neutron spectra from the Hiroshima and Nagasaki atomic bombs using a one-dimensional model and discovered that they differed considerably from the spectra used in calculating the T65 doses. Simple calculations based on these spectra suggested that the T65 neutron dose was markedly overestimated for Hiroshima. Subsequently, Loewe and Mendelsohn at the Lawrence Livermore National Laboratory (United States) and Kerr and Pace at Oak Ridge National Laboratory (United States) independently calculated the air doses at Hiroshima and Nagasaki and reported that both the neutron and the gamma doses differed substantially from the T65 estimates. These findings prompted a complete re-evaluation of the atomic bomb radiation dosimetry (for a fuller account of the events that preceded this reassessment, see [R20]). The reassessment, begun jointly by the Governments of Japan and the United States, culminated in March 1986 in a consensus system known as the Dosimetry System 1986 (DS86). The principal differences between this system and the T65 dosimetry, the heretofore most commonly used system (see Table 50), are as follows [R20]:

(a) the yield of the Hiroshima weapon is now presumed to have been approximately 20% greater than had earlier been thought; that is, 15 rather than 12.5 kilotons;

(b) although the free-in-air (FIA) gamma doses are somewhat greater at distances of 1.4 km or more in Hiroshima, neutron exposures are less in both cities. and substantially so in Hiroshima, about 10% of their previously estimated value (30% in Nagasaki). Since delayed radiation from the fireball makes a relatively greater contribution to the total DS86 dose, the loss or gain of shielding as a result of the blast effect, particularly in the first several seconds following the detonation of a bomb, could substantially influence kerma in shielded areas and, ultimately, organ absorbed dose. Time-dose dependencies have not, however, been taken into account either in this new system of dosimetry or the old;

(c) attenuation of the FIA gamma kerma by wooden Japanese structures, houses and tenements is approximately twice as great under the DS86 than under the T65 dosimetry (the average transmission factors under the two systems are 0.90 (T65) versus 0.46 (DS86) in Hiroshima and 0.80 versus 0.48 in Nagasaki). However, attenuation of the neutron kerma by such structures differs much less strikingly (the average transmission factors are 0.36 (T65) versus 0.31 (DS86) in Hiroshima and 0.41 versus 0.35 in Nagasaki);

(d) transmission of gamma rays through tissue is significantly higher, at least for the deeply situated organs, than had previously been estimated [K14]. It must be borne in mind, however, that in the T65 system each specific organ transmission factor is a constant averaged over all postures, orientations and ages; whereas in the DS86 system, fixed values are not used for the proximally or "heavily" exposed (defined as those survivors within 1,600 m in Hiroshima and 2,000 m in Nagasaki), where detailed exposure histories are generally available. Their organ doses reflect the circumstances of their individual exposures, including posture, orientation and age at the time of the bombing. The increased tissue transmission for most organs tends to offset, wholly or largely, the changes in the shielding transmission factors;

(e) finally, for some 18% or so of the exposed members of the Life Span Study cohort (largely individuals surviving in concrete buildings or factories), doses cannot as yet be computed, and the new dosimetry improves but does not clarify all of the implausibly high exposures seen with the T65 system. There remain a number of survivors whose estimated whole-body shielded kerma exposures exceed 4 Gy or, in some cases, 6 Gy. These are doses at or above the recently estimated LD95 in these cities [F13]; given the virtual obliteration of the immune system at doses in excess of 7 or 8 Gy, survival under the
circumstances that obtained in these cities would be most unlikely. Better means are needed to address these incongruities than the simple truncation of dose, since their inclusion in analyses can affect the shape of the dose-response relationship as well as estimates of its parameters [G13, G18, J6].

506. As previously seen with the T65 doses, a statistically significant increase in the frequency of deaths with increasing dose is observed for leukaemia, cancers of the oesophagus, stomach, colon, lung, breast, ovary and urinary bladder and multiple myeloma. No significant increase is as yet observed for cancers of the gallbladder, pancreas, uterus and prostate or for malignant lymphoma. The most recent report was extended to include other sites of cancer, such as bone, pharynx, nose and larynx, and skin except melanoma, but none of these sites showed a significant dose-response relationship [S49]; however, mortality from tumours of the central nervous system other than the brain tends to increase with dose (0.10 > p > 0.05). (mortality from brain tumours alone does not).

507. While the excess in leukaemia mortality has declined with time, it none the less remained significantly elevated as late as 1981-1985, showing that the period of risk is at least 40 years rather than the commonly supposed 25. For cancers other than leukaemia, excess deaths continue to increase with time in proportion to the natural cancer rate for the attained age, and the relative risk remains unchanged over time for all specific age cohorts except the younger, i.e., 0-9 years at the time of the bombings. For the latter cohort, unlike the older ones, the time from exposure to death is shortened with increasing dose for all cancers except leukaemia, and the relative risk decreases with time (Tables 51 and 52).

508. Tables 51 and 52 show the time course of excess risk in the DS86 subcohort data as a function of age at and time since exposure, for relative and absolute excess risk, in 10-year groups. The relative risk at 0 Gy changes significantly with time after exposure. The magnitude of this change is known only over a limited time period (about 40 years) since exposure.

509. Tables 53 and 54 give three summary measures of risk, namely, the excess relative risk at 1 Gy, excess deaths per 10^5 PYGy and the attributable risk. For all malignant neoplasms, leukaemia, all cancers except leukaemia, and eight specific sites of solid tumours based on the T65 and DS86 systems. These risks were derived by fitting a linear dose-response model to the data from both cities, both sexes and all ages at exposure within that subset of individuals in the Life Span Study sample for whom both T65 and DS86 doses are presently available (some 82% of all exposed individuals in the sample). Note that in so far as shielded kerma is concerned (Table 53), under the DS6 system, the excess relative risks are increased from 35% (stomach cancer) to as much as 53% (cancer of the ovary and other uterine adnexa). For excess deaths, the corresponding figures are 31% (multiple myeloma) and 61% (cancer of the ovary and other uterine adnexa). However, for no site or group of sites does the attributable risk change as much as 10%. For organ absorbed dose (Table 54), with the exceptions of cancer of the female breast or the ovary and other uterine adnexa, the risks are invariably lower with the DS86 doses and as much as 30% lower in the case of cancers of the stomach (excess relative risk).

510. Over the range of doses from 0-6 Gy, there is no clearly significant evidence of non-linearity (although other forms of response fit the data), so from a purely statistical point of view linear risk estimates are a reasonable summary of the dose-response. Moreover, when linear, quadratic, and linear-quadratic models (with or without provision for cell-killing) are fitted to the data on all cancers except leukaemia and on those five sites where a clear dose-response curve had previously been obtained (i.e., leukaemia, and cancers of the stomach, colon, lung and female breast), a simple linear model fits the data on leukaemia, cancers of the stomach, lung and female breast, and all cancers except leukaemia better than the quadratic model and as well as the linear-quadratic model, as judged by the deviance (that is, twice the difference in the log likelihoods under the full model, which exactly fits the data, and under the model based on the parameters that have been estimated). Inclusion of cell-killing does not significantly improve the fit, except in one instance where leukaemia mortality under either the linear or linear-quadratic model fits somewhat better with a cell-killing term. These findings hold true both for organ absorbed doses and shielded kerma.

511. Under the DS86 system, the neutron doses, although not wholly negligible, are so small that meaningful estimation of the neutron RBE is difficult, if not impossible. Reasonable RBE estimates cannot be derived directly through maximum likelihood estimation; however, some insight is possible if it is assumed that the small inter-city differences that still obtain reflect differences in neutron exposures. With the DS86 organ doses, assuming an equality of excess relative risk between Hiroshima and Nagasaki, the neutron RBE for leukaemia is 20-30; for all cancers except leukaemia, 30 or more; and for cancers of the stomach, lung and female breast, less than 1. Based on an equality of excess deaths between the cities, the neutron RBE for leukaemia or all cancers except leukaemia is 30 or more; for lung cancer, 10-20; and for cancers of the stomach and female breast, less than 1. The disparity between these estimates attests further to the difficulty of deriving meaningful estimates of the RBE with the new dose estimates for the survivors.

512. The differences between the cities are smaller under the new system than under the old for all sites of cancer, including leukaemia, and are no longer statistically significant. However, at face value, mortality in Hiroshima remains higher at most doses than in Nagasaki, for leukaemia as well as all cancers except leukaemia. This fact, when coupled with a similar consistent tendency for other indices of radiation damage (such as the frequency of chromosomal aberrations, lens opacities, and epilation), suggests that some explanation for the small inter-city difference in dose response is still necessary.
C. UNCERTAINTIES ASSOCIATED WITH RISK ESTIMATES

513. Even after many decades of study, the uncertainties that surround estimates of the carcinogenic effects of radiation are many and fundamental. Indeed, there is still no model of the underlying process that is clearly the correct one. The importance of a good theoretical model is greatest where the data are weakest, at low doses of low-LET radiation, so that our ability to estimate these risks is severely limited.

514. Because the majority of all cancers appear to have an environmental origin in the sense that avoidable exposure to environmental risk factors is involved [D13], much of this Annex has dealt with the problems in risk evaluation caused by the existence of multiple risk factors. In addition to environmental risk factors, there are also many host factors, such as genes, age, hormonal status, sex and the like, that affect risk.

515. It is probable that in any population exposed to ionizing radiation there is variation in the exposure to other risk factors. At low levels of radiation, this variation may be greater, perhaps much greater, than the risk produced by the radiation itself. It is not surprising that it is difficult to estimate risk at low doses or that different results are often obtained. The methods used to estimate confidence intervals tacitly assume that all exposed individuals in a given category (e.g., age, sex or dose) have equal risk, which seems unlikely to be true.

516. The most important documented other risk factor is smoking. Another source of bias is the "healthy worker effect": in occupational cohorts, workers are often healthier than the general population so that their baseline cancer rates may differ from the rates of the larger population, complicating the problem of determining the expected number of cases in these cohorts unless control groups from within the cohort are used.

517. The twentieth century has been a period of rapid change in levels of exposure to cancer-causing agents in all populations in which radiation exposure data are available. This is reflected in changing cancer rates within populations over time. All of the major cohorts used in radiation biology to estimate cancer risks have experienced changing exposure levels, though it has not been possible to account for this well in any study. Estimates of risk derived from cohorts that have been followed for the past half-century to the present will have inexact application to cohorts exposed now or in the future, and the degree of the inexactness is not known.

518. There is substantial variation in general mortality rates in different countries. Exposed individuals may be expected to experience somewhat different lifetime risks in a developing country as compared with an industrialized one. However, much of this difference in overall mortality occurs during childhood and would have little effect. Also, cancer rates for most sites are lower in developing countries, so that the absolute excess, and perhaps even the relative risks for the same dose, may be different. Most large population exposures studied to date have occurred in industrialized nations; there are few data and perhaps less exposure in the developing countries.

519. In addition to changing baseline cancer risks and the effects of other exposures, there is uncertainty over the dose-response pattern. Most current studies use a linear model for breast and thyroid cancer and a linear-quadratic model for other sites; these are the best-available models only, for the data do not really permit the validation of a specific model with confidence. It is unfortunately true that most estimates of low-LET, low-dose effects are based on extrapolations from high-dose data.

D. UNCERTAINTIES ASSOCIATED WITH RISK PROJECTIONS

520. The many uncertainties involved in the estimation of risk from observations on exposed cohorts have been reviewed in this Annex. The main limitations may be stated as follows: (a) no single large cohort has as yet been followed throughout its entire lifetime, so that the lifetime effects of exposure cannot be empirically determined; (b) the data that are available are most incomplete for those who were young at exposure; these individuals have not reached an advanced enough age for the bulk of their risk to be expressed, yet their lifetime risks may be the greatest; and (c) there are not now, and for the foreseeable future will not be, sufficient data on low doses to allow useful risk estimation.

521. In the face of these limitations, there are formidable problems in determining what model(s) to use in projecting risk forward into the unobserved future lifetimes of potential cohorts. Once the current cohorts have been completely observed, risk projection will have a sounder empirical basis.

522. The work of Muirhead and Darby [M36, M37], cited earlier, as well as models applied by the Radiation Effects Research Foundation (RERF) [S49], shows clearly that, depending on what covariates are considered and on how their effects are modelled, one can obtain strikingly comparable degrees of fit even to the best available data on the major exposed cohorts. In the Muirhead and Darby models, the parameter $\gamma$ expressed, at values of 0 and 1, the 'pure' multiplicative and additive projection effects; however, the most likely value of this parameter was sometimes statistically indistinguishable from either of these models under certain combinations of covariates. With an intermediate value of $\gamma$, the intuitive biological meaning of the model becomes unclear, and the model is probably best thought of as an empirical one only. Given this, it is clear, as noted in Muirhead and Darby [M37] that a variety of models could be constructed with approximately equivalent goodness-of-fit.

523. Although the goodness-of-fit of several projection models to the empirical data may be comparable,
their projected lifetime risks may not be as close. Being, therefore, currently unable to make lifetime projections with much confidence, alternative models have to be presented, which, hopefully, bracket the true risks. Even so, there is no way of specifying quantitatively the degree of uncertainty in these alternatives.

524. Until very recently, it had appeared from experimental animal data and empirical data on humans that the relative risk projection model was the more appropriate of the two models for most solid carcinomas. However, if the excess risk of these tumours eventually declines with advancing time since exposure, as some data now suggest, then neither simple additive nor simple multiplicative projection effects will pertain, and none of the models, even hybrid models such as those of Muirhead and Darby, which describe the effects of time since exposure in a monotonic way, will be applicable.

525. These are fundamental problems, for it does not currently appear possible to discriminate among the various projection models based on their fit to empirical data. The only practicable solution to this problem may be to wait until the experience of the Japanese, the spondylitics and the other cohorts is more fully expressed than at present and to derive empirical projection models. Even so, changes in baseline risks, as well as confounding cancer risk factors, may make such projections inaccurate for future cohort experiences.

VII. RISK PROJECTIONS

A. GENERAL CONSIDERATIONS

526. In chapter II of this Annex, the various concepts related to risk projection, the kinds of data required, and past efforts to estimate lifetime risk from exposure to ionizing radiation were discussed. In this chapter, the most appropriate existing data will be used to compute estimates of lifetime risk for those cancer sites for which sufficient information exists to make meaningful projections. The purpose is to derive approximate estimates of the risk of exposure to low-LET radiation, taking into account sex, age at exposure and time since exposure for the lifetime of an entire exposed population.

527. Radiation-induced mortality in a population may be represented in a number of ways, most commonly as either the expected lifetime number of excess cancer deaths in the exposed population or the number of person-years of life lost because of cancer deaths, both per unit collective dose. Estimation of these expressions of risk remains formidable, as does a meaningful synthesis of the estimates that are already available. The task is complicated by one or more of the following main difficulties: (a) the unique nature of some of the samples from which risk coefficients have been derived; (b) the differences between studies in sample sizes and in the periods of follow-up; (c) the methods of case ascertainment that have been employed; (d) the poor knowledge of the doses received and their distribution over sites; and (e) the nature of the comparison groups used.

1. Whole-body risk coefficients

528. Some of the numerous studies described elsewhere in this Annex, although important in their own right, are of limited value for projection purposes; they provide the relative frequency of occurrence of cancer in an exposed group, as contrasted with a non-exposed referent one, but often at only one of the many sites of interest, and the dosimetric uncertainties make estimates of the risk of cancer per unit dose difficult. Commonly, doses in these particular cohorts have been concentrated in one part of the informative range for estimating dose-response patterns, making it difficult to estimate effects at low or intermediate doses. Three studies, namely, those of the ankylosing spondylitics patients [D11, D21], the women treated with radiotherapy for cervical cancers [B12] and the survivors of the atomic bombings of Hiroshima and Nagasaki [S48, S49], have been the bases for estimating the frequency of occurrence of cancer, per unit dose, at multiple sites of malignancy. But, even here, however, derivation of a combined risk coefficient is difficult and has not been attempted.

529. While these three studies agree generally in identifying the sites at which the frequency of cancer is elevated following exposure to ionizing radiation, the study-specific estimates of the excess relative risk for specific malignancies per unit dose, based on the information currently published vary, particularly in so far as the cervical cancer series is concerned. There are numerous reasons why this should be so, but especially pertinent are the conditions of exposure, the nature of the dose data presently available, differences in the age or sex distribution of the exposed individuals in the study samples, the dissimilar periods of follow-up, and the background rates used to compute the expected number of cases. Table 55 summarizes the main characteristics of these three studies and illustrates the differences between them in the respects just enumerated. These points were reviewed in chapters III and IV.

530. Exposure of the patients with cervical disorders or ankylosing spondylitics occurred because of illness; this was not the case among the Japanese survivors. The reasons why these patients may not be representative of the general population were discussed in chapter IV. In the two patient series, exposure was to either x rays or gamma rays, whereas the atomic bomb survivors received a mixed dose of gamma rays and neutrons, albeit primarily the former. The Japanese sample alone includes a full representation of sexes and ages; the other two studies are restricted either wholly or largely to one sex, and they do not include a sufficient number of individuals below the age of 25 at the time of exposure, when the excess relative risk appears to be larger, to provide an estimate applicable to a general population. Individual estimates of dose are not available for all (or even the majority) of the patients with cervical disorders or ankylosing spondyl-
ititis. Risk coefficients have been derived from the mean dose among a 7% random sample of the spondylitis patients, and dose-response estimates, based on the individual doses received by the cervical cancer patients in that series, encompass only a subset of the patients. However, mean doses are often poor descriptors of the dose distribution, notably among cancer patients, because of the highly skewed nature of the individual doses and their wide range. As to the periods of follow-up, the maximum length of follow-up of the first sample members is similar in the three studies, but since enrolment proceeded over a longer period of time in the two patient series, the mean years of surveillance for them is substantially shorter than for the atomic bomb survivors. In terms of sample size, the atomic bomb survivors and the cervical cancer series are approximately equivalent, but the number of the person-years at risk in the study on the atomic bomb survivors is much larger. In the cervical cancer and spondylitis series, unlike the atomic bomb survivors, the variation in doses among exposed organs is very different, because the treatment was concentrated on one part of the body. This makes whole-body equivalent dose estimation difficult. There have also been marked changes in the nature of x-ray equipment and in therapeutic methods. Finally, there are differences in the nature of the referent groups in the three studies: these were thoroughly discussed earlier in this Annex (see chapters I and III). A summary of the excess relative risks per gray obtained in these three studies is provided in Table 56.

531. A special feature of the atomic bomb survivors is that they received exposure from low-LET radiation and from neutrons simultaneously. It is important therefore to consider how the projections to follow would be affected by the assignment of either a fixed or a dose-variable RBE for neutrons, relative to gamma rays. Figure XIX provides, in graphical form, the change in the estimated number of excess deaths with fixed values of RBE varying from 1 to 20. It will be noted that the risk coefficients for both leukaemia and all cancers other than leukaemia become smaller as the assigned RBE increases. Over the range of 1 to 20, the risk estimates based on shielded kema diminish by about 54-72%; however, the estimates based on organ dose equivalent diminish by only 15-20%, reflecting the higher transmission values associated with gamma- and neutron-radiation under the DS86 system of dosimetry. Elsewhere, Shimizu et al. [548] have shown that the use of a variable RBE, one changing as a multiple of the inverse of the square root of the neutron dose, would have an approximately equivalent effect on the projections. Thus, for example, the estimate of the excess deaths from leukaemia, using an RBE equal to 1/1 Dn, where Dn is the neutron dose in gray, is 2.93; whereas that based on an RBE equal to 20/1/2 Dn is 2.47. Similar changes occur for excess deaths attributable to cancers other than leukaemia: the risk coefficient changes from 10.08 to 8.86 excess deaths per 10^4 PYGy, or slightly less than 20%.

2. Site-specific risk coefficients

532. In addition to the three studies that involved (albeit under different conditions of exposure) the simultaneous irradiation of many tissues in the body and from which risk estimates could be extracted and their relationships analysed, there are a large number of other studies in which single tissues were exposed to radiation for a variety of purposes and from which risk estimates to individual tissues have been derived, as reviewed in detail in chapter III. The risk coefficients resulting from these studies are summarized in this section.

533. Since the UNSCEAR 1977 Report [U2], in which radiation carcinogenesis in humans was last reviewed, several organizations have estimated summary risk coefficients (absolute or relative) for a variety of major organ sites. These include studies by BEIR III [C4] in 1980 and by the United States Nuclear Regulatory Commission in 1985 [G11], and the United States National Institutes of Health, also in 1985, in the radiobiological tables [U3]. Their reports attempted to combine the literature available at the time. The BEIR III Report synthesized individual studies along with the most recent Japanese data then available; Gilbert [G11] and the radiobiological tables relied heavily on BEIR III, modifying their estimates according to a few other reports but mainly basing them on the then-latest data from the patients treated for ankylosing spondylitis and the atomic bomb survivors. Each of these studies, to which the reader is referred, discussed the reasoning behind its respective site-specific coefficients. For comparison purposes only (because the information on which they are based is now out of date), the summary risk coefficients for each study are given in Tables 4 and 8 [C4, G11].

534. Because these studies appeared in the period 1980-1985, they could not include the results of the latest data and dose revisions in Japan [R20, S49] and
in the spondylitis series [D21, L16], nor could they include the recently published risk coefficients from the cervical cancer series [B36, B38]. Site-specific risk information from the most recent studies is given here in Tables 26, 46, 51, 52, 53 and 54. These tables provide the current estimates of risk from the three largest studies based on age at exposure, time since exposure and sex. The scientific details of these studies were discussed earlier, along with the limitations and specific characteristics of each study population.

535. Chapter III of this Annex reviewed many other studies in which site-specific risk coefficients were estimated. While they vary greatly in their particulars, e.g., sample size and the like, it is worth summarizing the risk coefficients from these studies. For each site, reference will be made to the tables and figures, discussed in chapter III, that provided the best data on risks. Also, the principal bibliographic references for each site will be given, as will be the general range of risk estimates from other studies not already included. Note that the estimates in the following summary that are derived from the Japanese or spondylitics are based on the old dosimetry and do not include the most recent data reports (these values are given in Table 56).

536. Leukaemia. While many studies of different types of exposure have found an excess of leukaemia, the best risk coefficients come from the spondylitics patients [D21, L16, S31], the Japanese data [S48, S49], and, very recently, from the marrow-weighted study of cervical cancer patients [B36]. These individuals received exposures to external low-LET radiation. The risk coefficients are included in Table 56. Some other dose-response data, from gynaecologic patients, were summarized in Table 31. The BEIR III Committee estimated the absolute risk coefficient for brief exposure in childhood to be about 0.01-2.2 excess cases per 10^4 PYGy [C4; see Tables V-17 and V-18], and Ron and Modan [R1] estimated absolute risk to be 0.60 male and 0.87 female cases for the same unit of exposure, although this difference was not statistically significant.

537. Multiple myeloma. Risk coefficients for multiple myeloma are summarized in Table 32. The most important reference for these data is [C10]. A recent estimate from Japan gives 0.48 incident cases per 10^4 PYGy bone marrow dose [H5, 12]; however, the latter estimate is based on the T65 dosimetry.

538. Bone. Table 33 provides a summary of risk coefficients for bone cancer based on an analysis by BEIR III [C4]. Figure VIII presents dose-response data. Other estimates for gamma-emitting radionuclides are 2.0 excess cases per 10^4 PYuCi for long-half-life isotopes (absolute); 1.8 (children) and 1 (adults) for short-half-life isotopes; and for alpha-emitting radionuclides (absolute) 200 per 10^4 PYGy [T11]. There are many cases of bone cancer in exposed children, but dose-response estimates are unreliable relative to a general population since most of the children, exposed during treatment of retinoblastoma, are genetically susceptible to osteosarcoma even in the absence of irradiation (see section III.B).

539. Breast. There are no data on breast cancer in males. Tables 36, 37 and 38 summarize the details of risk coefficients from a variety of studies. For adult exposures, the range of absolute risk coefficients is 3·10^{-10} to 10^{-8} PYGy, and that of relative risk coefficients is 2·5. For juvenile exposures the data are less reliable, but absolute risk coefficients are 3·8 per 10^4 PYGy [B6, T6] and the excess relative risk at 1 Gy, based on death certificates, is about 0.69 in the most recent T65D data from Japan [P15].

540. Thyroid. Thyroid cancer risks (incidence) are summarized in Tables 20, 21, 22 and 39 and in Figure 1. Other estimates are 1·4 per 10^4 PYGy [C4, Z3] for adults and 1·5-9·5 for children [S13, S38], as judged by a variety of studies, including those of exposure to fallout. A major recent report discusses thyroid cancer induction in detail [N5]. There is about a 3:1 sex ratio of cases, with females predominating, and it has been estimated that only about 10% of all cases become fatal; many benign tumours also arise. The latency period for fatal cancers appears, however, to be very long (even up to 40 years or more), so that the current data may still be incomplete.

541. Skin. Satisfactory summary risk estimates for skin cancer incidence do not exist. The BEIR III estimates (see [C4], Table A-32) of between 0.44 and 1.02 cases per 10^4 PYGy, based on scalp and thymus irradiation, are not consistent with the chest fluoroscopy data. In uranium miners, Secv [S51] has estimated one excess case of basal cell carcinoma of the skin per 10^4 PYs. Information is not yet available from Japan.

542. Lung. Other than the Japanese and spondylitics patients, the best data on lung cancer are derived from individuals who inhale alpha-emitting radionuclides. Most data come from males, except in Japan, and the occurrence of this cancer is seriously affected by smoking interactions; there is as yet no consensus on whether the effects of smoking are more additive in nature or more multiplicative. Thomas and McNeill's [T11, T20] summary of these risks is provided in Table 10. These absolute risk coefficients are in units of million person-years per working level month (WLM); as discussed earlier, an approximate factor for converting from cases per 10^4 PY WLM to cases per 10^4 PYGy is 1.67 (with 1 WLM corresponding to 6 mGy absorbed dose in the bronchial tree). The absolute estimates range between 5 and 50 cases per 10^4 PYGy. As noted in chapter III, even when they are based on the same data, the estimates do not always agree, and they must be treated as uncertain. Most estimates of relative risk from brief external exposures to doses of less than 10 Gy are 1·2-2·0. Full treatments of risks to the lung will be found in [C20, 111].

543. Digestive system. The estimates presented from Japan and the spondylitics patients (see Table 56) constitute the best information available on most digestive system cancers. As previously discussed, the data from the spondylitics patients are not reliable in regard to co-loctal cancer because of the high spontaneous rates of co-loctal disease, and the results from studies of pelvic irradiation to treat gynaecological disorders are inconsistent and appear
to be affected by cell sterilization and other biological or environmental effects. Most liver cancer data come from internal emitters, particularly the Thoroughbred patients. The Japanese and the spondylitis patients show uncertain results, and neither the studies by themselves nor their joint analysis has found an excess sufficient to derive useful risk coefficients (the BEIR III best estimate is given in Table 4). The liver is a site of frequent metastasis, and risk estimates may confound primary and secondary hepatic cancers.

544. Salivary glands. Detailed risk coefficients for salivary gland cancers, based on results of many studies, are given in Table 42. These were derived by Land [L11] in a summary analysis of this site. Land estimated the best overall absolute risk coefficient for this site to be $0.26 \pm 0.06$ cases per $10^4$ PYGy. A recent estimate from Japan, based on T65 dosimetry, is $0.056 \pm 0.036$ per $10^4$ PYGy [O4, T15].

545. As has been noted, the inter-study spread of values observed for single tissues is large. Sometimes very large, presumably owing to the differences mentioned in paragraph 527. There is no fully satisfactory way to make suitable allowance for these differences in generating a combined estimate. Thus, there are only two options: either to combine the data without regard to the important differences enumerated above, a step that does not appear defensible; or to select the best possible set of estimates from among the various studies. Therefore, the Committee compares in the section to follow the data from the atomic bomb survivors, the ankylosing spondylitis series and the series of patients irradiated for cervical cancer.

### B. SUMMARY OF RISK PROJECTION METHODS AND RISK ESTIMATES

546. The projections by the Committee will consider the induction of leukaemia and other cancers separately, drawing from the atomic bomb survivors and the ankylosing spondylitis and cervical cancer patients. Estimates are computed at 1 Gy of high dose rate exposure based on a linear dose-response model in the case of solid cancer. Data on leukaemia in the spondylitis and cervical cancer series take account of cell killing. The Committee has adjusted for this fact in the estimate it used to project the lifetime risk among the spondylitis patients but could not do so in the case of the cervical cancer series. Separate estimates are computed from an additive projection model and a multiplicative projection model, using the life-table methods and minimum latency periods described below. These methods are similar in concept to those used by the BEIR III Committee [C4] and by the Nuclear Regulatory Commission of the United States [G1]. Although details differ, largely to accommodate new data. It has generally been presumed that the additive and multiplicative models encompass the range of reasonable projections; however, Muirhead and Darby [M36, M37] have questioned whether this is true. As was seen in chapter II, they contend that it is difficult, given current data, statistical methods and biological theory, to choose between the additive and multiplicative models, or to determine some intermediate ones.

547. In addition to excess cases per 1,000 persons exposed to 1 Gy, estimates will be provided of lost life expectancy in person-years per 1,000 persons.

### 1. The basic projection model

548. The lifetime risk coefficients estimated in this chapter have been computed using an interactive, parametric demographic projection model developed by the Centre d'Etude sur l'Evaluation de la Protection dans le Domaine Nucléaire (CEPN, France) in 1985. It employs classical double-decrement life-table techniques and is not dependent on the data or assumptions used in the present calculations. The model is sufficiently general to permit a wide range of choice of demographic, epidemiological and biological data or assumptions. Several kinds of computations can be made, including: (a) the effect of a single exposure on a cohort of a given age and sex, and (b) the effect of a single exposure to a given population of mixed ages and sexes.

### 2. Analytical expression of the model

549. The analytical formulation for calculating lifetime risk is the following: at age a and for a dose D, the absolute excess mortality rate $V(a,D)$ is considered. If an exposure at age $a_1$ is assumed, the corresponding lifetime risk

$$U(a_0,D) = \int_{a_0}^{100} V(a,D)[N(a,D)/N(a_0)]da$$

where $N(a,D)/N(a_0)$ is the probability of survival to age a for an individual alive at age $a_0$, taking into account the risk of mortality both from radiation-induced cancer, and from all other causes.

550. To compute this lifetime risk, the studies on irradiated populations provide the following risk coefficients: (a) the absolute excess mortality rate, $I(D)$, and (b) the excess relative risk per Gy, that is $K(D)$.

551. The following two expressions for $V(a,D)$ are associated with the additive (absolute) and multiplicative (relative) projection models, respectively:

$$V(a,D) = I(D) \int_{a_1}^{a} [N(a,D)/N(a_0)]da$$

$$V(a,D) = K(D)C(a)$$

where $C(a)$ is the baseline cancer mortality rate in the population for the sites under consideration.

552. Thus, the lifetime risk estimates can be expressed as follows:

**Additive risk projection model**

$$U_a(a_0,D) = I(D) \int_{a_1}^{a} [N(a,D)/N(a_0)]da$$

**Multiplicative risk projection model**

$$U_a(a_0,D) = K(D) \int_{a_1}^{a} C(a)[N(a,D)/N(a_0)]da$$
where \( L \) is the minimum latency time and \( P \) the plateau period (i.e., the period of time following exposure during which manifestation occurs, and over which the risk is presumed to be constant). It should be noted that this method of estimating lifetime risks is essentially the same as that employed in the BEIR III Report [C4] and in the NUREG Report [G1]. An alternative approach would be to calculate separately the total number of cancers occurring in a lifetime in an exposed and a non-exposed population, and to take as the excess number of cancers the difference between these totals. The latter method would result in a smaller number of excess cases, for it excludes from the excess that fraction of cases which would have developed cancer for non-radiation related reasons at a later date.

3. Calculation of the loss of life expectancy

553. Using the same notation as in paragraph 549, the life expectancy at age \( a_0 \) (i.e., the average survival time for individuals alive at age \( a_0 \)) is given by

\[
\int_0^{100} \frac{[N(a,D)]/[N(a_0)]} {da}
\]

If this is computed both assuming no radiation exposure and assuming exposure at dose \( D \), the difference between the two quantities is the loss of life expectancy due to exposure.

4. Demographic and background epidemiological data required

554. The characteristics that must be known for the population under study are the following: age and sex structure, overall mortality rate and cancer mortality rate by site. Since the model uses a year as the time-scale of interest, annual values are obtained by linear interpolation from the published information (which is generally presented in age intervals of 5 or 10 years). The survival rates are computed from current mortality rates and the projections assume that these will not change in the future.

5. The computational process

555. The principle of the model is to compute, by a discrete time analog of the basic demographic equation, for every year, \( i \), the numbers of alternative outcomes possible for survivors through the previous year, \( i - 1 \). (that is, the numbers of fatal cancers at each site under observation, of deaths related to all other causes and of survivors to the next year). The first value is calculated and serves to increment the cumulated number of cancer cases already computed for the previous years and then to modify the baseline life-table. This calculation is limited to the assumed period of expression of excess cancer risk after the exposure. This period depends on the site or tissue under consideration; the minimum latency period has been taken to be 2 years for leukaemia and 10 years for all solid cancers. The plateau durations are assumed to be 40 years and lifetime for all cancers except leukaemia and 40 years for leukaemia. The number of survivors at age \( i + 1 \), \( N(i + 1) \), is equal to the number of survivors at age \( i \), \( N(i) \), minus the number of those who die from baseline mortality, minus the number of those who die from radiation exposure.

6. Reference population

556. The reference populations considered here as the bases for the lifetime projections are the current general Japanese population for the atomic bomb survivors, the current adult male population of the United Kingdom for the spondylitis patients and the current adult female population in the United Kingdom for the cervical cancer series. The first two populations were selected since the studies were carried out in these two countries. The adult female population of the United Kingdom has been assumed to be representative of the other populations among which the cervical cancer study was conducted. The validity of extrapolation to other populations will be considered later.

7. Risk coefficients

557. The excess risk coefficients for the atomic bomb survivors are those based on the DS86 subcohort, as in Table 54. These coefficients were derived by the authors [S48, S49] on a linear relative risk model, using organ absorbed doses from the explosions, and are restricted to mortality. The RBE of neutrons was assumed to be 1 in their estimation procedure. The coefficients represent mean values for both cities, both sexes (except for the breast and ovary), and all ages at the time of the bombings combined. The sites of cancer that have been selected for risk projection are those for which a statistically significantly increased mortality with increasing dose has been shown: namely, the bladder, breast, colon, leukaemia, multiple myeloma, oesophagus, ovary and stomach. Thyroid, lung and bone will be discussed later. For the spondylitis and cervical cancer series, the risk coefficients are given in Table 56. It is important to note, first, that in all three instances the risk coefficients that are used have been obtained from published reports and do not take into account the underreporting of cancer deaths on death certificates. BEIR III [C4], in its projections, increased these coefficients by 25% to take account of underreporting. A comparable action here would increase the Committee's projections of excess lifetime mortality by 20-25%. Second, and specifically with respect to the risk coefficients derived from the atomic bomb survivors, there is a levelling off, or a plateauing of the risk at shielded kerma of approximately 4 Gy and higher, and thus a linear relative risk model fitted to the full array of observed doses may underestimate the risk at doses below 4 Gy (approximately 3 Gy in organ absorbed dose). When the risk is estimated based on shielded kerma of less than 4 Gy, the excess deaths per 10^4 PYGy are approximately 5% higher for leukaemia,
and 15% higher for all cancers except leukaemia [S48].

558. Two kinds of coefficients are used as input, as in Table 54; these vary with the type of model chosen for the lifetime projection: the excess relative risk per Gy is used for the multiplicative projection model (constant relative risk) and the excess mortality per 10^4 PYGy is used for the additive projection model (constant absolute risk). In all cases, both the multiplicative and the additive projection models have been used, for comparative purposes (even though, as discussed earlier, for some sites one model appears to be more realistic than the other). Use of the two models in this context is not meant to imply any description of causative biological processes; the models are simply used to derive lifetime risk projections.

8. Indexes of harm

559. The indexes of harm have been restricted to different expressions of the effects of excess mortality associated with radiation-induced cancers in a lifetime after exposure. Two indexes are presented. The first is the lifetime excess number of fatal cancers, and the second is the loss of life expectancy in a population of 1,000 persons exposed at various ages to a single dose of 1 Gy of low-LET radiation at a high dose rate to each tissue.

560. Although the values of the indexes are calculated by the Committee at 1 Gy, values may be computed at other doses, provided the shape of the basic dose-risk relationship (linear, linear-quadratic, etc.) is known.

9. Treatment of uncertainty

561. The risk coefficients given in Tables 54 and 56 are accompanied by their 90% confidence intervals, when available. The upper and lower 90% statistical confidence intervals of these coefficients have been used to calculate the uncertainty inherent in the indexes of harm. It must be emphasized that this does not encompass the total uncertainty associated with the projections but only the statistical one attributable to the risk coefficients used as inputs. Uncertainties on dose and on demographic variables are not considered explicitly.

10. Fractionated and low-dose-rate exposure

562. The risk coefficients derived from the Life Span Study and given in Table 54 relate to instantaneous exposures to moderate to high doses and in principle represent only such exposure conditions. As shown in Table 55, irradiation of the cervical cancer patients was protracted over a few days or weeks, and that of the spondylitis patients was fractionated over a few weeks. For low-dose rates, an appropriate correction factor should be used if the indexes of harm are to reflect the experience coming from such epidemiological and experimental conditions.

C. RESULTS OF PROJECTIONS

563. The projections that follow should be prefaced by some statements about the approximations inherent in the model adopted. First, the Committee's lifetime projections are based on a simple modelling procedure, and deliberately so. More complex models could have been used and more effort to adjust for the known shortcomings in the data could have been made, but with each such ad hoc adjustment the results would have become progressively more particular and less and less applicable to the broad community of countries to which the Committee's deliberations are directed. As an illustration, the risk coefficients the Committee has employed are based on deaths reported to be due to the presence of a malignancy. Death certificates, however, are known to underreport the deaths that actually are attributable to cancer. An adjustment could have been made to account for this underreporting, but the Committee has not done so, for the degree of underreporting will undoubtedly vary from country to country.

564. The Committee has used other simplifications. Among these are age-constant risk coefficients (absolute or relative) that do not change with time following exposure (after the minimal latency period) or with age at exposure, as well as stable age-specific rates of mortality ascribable to cancer and other causes. The Committee has also ignored possible differences in mean survival time after the diagnosis of a malignancy as a consequence of different medical standards in different countries and their evolution with time. Again, while the model used could accommodate other assumptions, the data are still too sparse or contradictory to provide alternatives confidently. For example, the observations on the patients with ankylosing spondylitis suggest that the relative risk coefficient for all cancers other than leukaemia declines with time after exposure [D21], but this has not been seen, at least as yet, among the atomic bomb survivors of Hiroshima and Nagasaki [S49], except for those exposed as children. If the relative risk does in fact decline, then the Committee's projections will overestimate the lifetime risk. Similarly, if mean survival time of cancer cases increased, the loss of life expectancy would decline, although the total number of cancers would not change much (some diminution would be expected, however, as a result of the increased mortality from competing causes).

565. The coefficients assumed for the computations have been derived by linear regression analysis in the case of the atomic bomb survivors, the ankylosing spondylitis patients, and the cervical cancer series with cell-killing correction for leukaemia in the latter case. The model used by the Committee to project lifetime risks of cancer mortality or life span shortening at 1 Gy of low-LET irradiation administered at a high dose rate does not require selection of any given function of the dose-response relationship and therefore the Committee has not imposed any pre-selected function on the original data in order to derive its two projections.

566. For reasons of convenience, the Committee will consider separately the projections for the adult
population (males and females over 25 years of age), where comparisons among the three studies cited in paragraph 528 are possible: and the young population (below 25 years of age), for which the only reliable risk estimates are those that come from the atomic bomb survivors.

1. The adult population

567. The Committee’s projections were carried out according to the assumptions given in Table 57. To allow a comparison of the results of the three studies cited in paragraph 528, the basic assumptions need to be adapted somewhat. First, the atomic bomb survivors study comprises individuals of both sexes and all ages, which the other two studies do not (see Table 55). Consequently, for a meaningful comparison, it has been necessary to examine only the adult population in the Japanese series. This means that the basic risk coefficients shown in Table 56 had to be modified to take into account the subtraction of the young cohorts. It is these modified figures for the absolute excess death per 10⁶ PYGy, shown in Table 58, that have been used in the computations that will follow. Of necessity, since the requisite risk coefficients have not been published for the adult population only (nor for the working population, defined as aged 25-64), the Committee has been obliged to use excess risk coefficients based on averaging the sex-specific risks within the age groups 20-29, 30-39 and above 40, and weighting these averages by the proportion of the population within each of the age groups. To estimate lifetime risks in the working population, the Committee has used the risk coefficients derived from all ages and both sexes. Figures of the ankylosing spondylitis and cervical cancer series, which were not corrected, are also shown in Table 58. Second, the cervical cancer series refers only to females, so a female population (that of the United Kingdom) has been taken as the reference; similarly, the spondylitis cohorts are mostly males and therefore the male population of the United Kingdom has been adopted as a referent. Thus, the results of the extrapolations from the Japanese and cervical cancer series should be compared only in the female population, and the results from Japan and the spondylitis series should be compared only in the male population. Third, for cancers other than leukaemia, a comparison is only possible among two of the series, because no appropriate risk coefficient can be derived from the cervical cancer series. The spread of doses between the heavily irradiated pelvic organs (where cell sterilization could be important) and the organs in the upper part of the body (which received very low doses) is so large that risk coefficients based on averaged absorbed doses would have no meaning. These reservations also apply, though to a lesser extent, to the spondylitis series; however, since the authors [161] provided an average whole-body dose (in addition to excess relative risk [D21]), the computations were made using these summary figures.

(a) Excess lifetime mortality: leukaemia

568. Table 59 shows the results of the Committee’s projections, based on the model and assumptions described, in respect to excess lifetime mortality for leukaemia using the risk coefficients for each of the three major series (Table 58). Under the multiplicative risk projection model, the risk estimates range from 2.8 to 8.1 for females and 9.0 to 14 for males, and under the additive risk projection model from 1.4 to 7.0 for females and 4.4 to 13 for males (excess cases per 1,000 persons at 1 Gy of high dose rate low-LET exposure). Even considering the problems with the risk coefficients in these series, discussed earlier, these values are all well within an order of magnitude of each other.

(b) Excess lifetime mortality: all cancers other than leukaemia

569. Only two of the three general series the Committee has cited give usable estimates of the excess risk of cancers other than leukaemia, namely, the atomic bomb survivors and the patients with ankylosing spondylitis. For the assumption of a lifetime plateau (lower half of Table 59), the estimates of these two series are within a factor of about 2 to 4, the figures being lower for the series on the ankylosing spondylitis patients as compared to the Japanese atomic bomb survivors. It is tempting to speculate that this difference in risk relates to the modality of irradiation being instantaneous for the atomic bomb survivors and fractionated over a few weeks for the ankylosing spondylitis patients. Although this phenomenon is suggested by the data and by no means demonstrated, it is in the same direction that would be in agreement with a large body of radiobiological literature, reviewed most recently in the UNSCEAR 1986 Report and in reference [N1]. This shows that dilution in time of the dose yields generally lower effects than for the same dose delivered at high dose rate and/or without fractionation.

570. When the mortality from leukaemia is combined with that from all other cancers, assuming a plateau of 40 years for leukaemia and a lifetime plateau for all other malignancies (after the minimum latency), between 46 and 56 additional cancers would be expected in a population of 1,000 adults (500 males and 500 females), based on the Japanese risk coefficients, under the additive and multiplicative projection models, respectively.

(c) Loss of life expectancy: leukaemia

571. Table 60 shows the results of the projections in regard to loss of life expectancy attributable to the additional cases of leukaemia. The results are quite similar to those for excess lifetime mortality; namely, all three series provide estimates in generally good agreement. The spondylitis patients and the Japanese-based estimates under the multiplicative model are in fact very similar. Even the greatest discrepancies, between the cervical cancer and the other series, are within a factor of about 5.

(d) Loss of life expectancy: all cancers other than leukaemia

572. Taking the figures in the lower half of Table 60 as the most conservative ones, the projections derived from atomic bomb survivors are two to about four
times as great as those based on the ankylosing spondylitis patients. Life lost calculated by the additive risk projection model is higher than that calculated by the multiplicative risk projection model, but not by much.

573. As Table 60 shows, the expected number of person-years of life lost from all cancers would be about 840 for the additive model and about 620 for the multiplicative model for irradiation of 1,000 adults (500 males and 500 females), based on the Japanese risk coefficients, under the conditions described in Table 57.

574. It warrants reiteration that the absolute values given so far for irradiation of an adult (over 25 years) population apply to 1,000 persons of both sexes when a constant risk coefficient is used.

2. The population of children as a part of the population

575. The epidemiological evidence accumulated to date strongly suggests that the initial relative risk of subsequent malignancy following exposure to ionizing radiation is appreciably higher when exposure occurs early in life (within the first two decades after birth). From what is so far known about the biological aspects of cancer induction, this finding is not unexpected. However, apart from the data on the youngest age at the time of the bombings cohorts in the Japanese Life Span Study, there are few data from which specific risk coefficients can be derived, and even among the Japanese survivors the coefficients available are based on small case numbers and have relatively large sampling errors. These cohorts, furthermore, are those with the largest expected numbers of years still to live, and it is far from clear whether the high excess relative risks presently seen will persist. It is true that the Japanese data suggest a declining risk, both for leukaemia and all cancers except leukaemia, notably among survivors exposed before the age of 10 (the trends seen in Tables 51 and 52 for the 0-9 age group are statistically significant). These cohorts have only recently entered those years of life when the background rates for virtually all solid tumours, as well as for the chronic forms of leukaemia, increase markedly. Thus, it will be several decades before their cancer experience as middle-aged and older-aged individuals is clear. This poses a dilemma for the projection of lifetime risks. On the one hand, it would be unwise to assume that the risks will decline, for if they did not, the indices of harm could be grossly underestimated. On the other hand, to assume that these excess relative risks will persist throughout life, if in fact they do not, will project a harm that is much too high for these cohorts. It is largely for these reasons that the Committee has elected to examine the childhood population separately.

576. There are two separate aspects of the irradiation of young cohorts: first, their apparently greater susceptibility to the carcinogenic effect of radiation (this aspect can be studied by a discussion of the declining risk coefficient as a function of age) and second, their longer life expectancies relative to adults and the correspondingly longer time during which the consequences of exposure may be expressed.

577. The first aspect has already been considered in Tables 51 and 52. These Tables present excess relative risks and excess deaths for the atomic bomb survivors (which is the only series for which such estimates, although preliminary, are so far available) as a function of age at exposure and age at time of death, separately for leukaemia and all other cancers. The limited experience does not warrant analysing this phenomenon site-specifically.

578. The second aspect, as it applies to the population of Japan, is illustrated in Table 61. Since the risk coefficient has been presumed to remain constant over all ages, the impact of the demographic component introduced by the younger cohorts may be perceived from this Table.

579. The main difficulties in assessing the impact of exposure on the young arise when one attempts to evaluate the interaction between these two aspects for the purpose of calculating an overall measure of risk for the whole population, considering each age class separately. In fact, each age class will be characterized by its own coefficient of risk and its own demographic future. Since it appears from Tables 51 and 52 that the excess relative risk does not systematically change for ages above 20, and certainly not for ages above 30 (at least for solid cancer), the Committee has not attempted to calculate the whole extent of these changes. It should be pointed out that the observed values at the younger ages, based as they are on a relatively small number of cases, have large and unequal sampling errors. Previous attempts to take age-related coefficients into account have relied solely upon a statistical smoothing of the observed values. The Committee believes, however, that the observed changes in susceptibility as a function of age are not related to time alone, but also to the biological stages in development that are unique to certain ages, such as puberty and its associated hormonal changes.

580. Under these circumstances the Committee decided to make two separate sets of projections, using the multiplicative and the additive projection models: (a) the lifetime excess mortality and loss of life expectancy as it applies to a population for which the same risk coefficient is taken for all ages and (b) the lifetime excess mortality and loss of life expectancy as it applies to a population at ages 0-9 and 10-19, with coefficients specific for these age groups. These latter coefficients are as follows:

<table>
<thead>
<tr>
<th>Age at irradiation</th>
<th>0-9</th>
<th>10-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excess relative risk</td>
<td>19.1</td>
<td>4.5</td>
</tr>
<tr>
<td>Excess deaths</td>
<td>3.42</td>
<td>1.52</td>
</tr>
<tr>
<td>Other malignancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excess relative risk</td>
<td>1.56</td>
<td>0.96</td>
</tr>
<tr>
<td>Excess death</td>
<td>2.77</td>
<td>6.16</td>
</tr>
</tbody>
</table>

These values have been taken from [S49] (Appendix Tables 5a and 5b), averaging over the two sexes.
581. For the multiplicative model and for excess lifetime mortality, the difference in the final effect introduced by using a measure of risk related to the specific age at exposure rather than a constant risk, that is a risk averaged over all ages and exposure, can be substantial. The computations show that one obtains three to four times more deaths due to leukaemia and all other cancers for the ages 0-9 at the time of exposure by using the age-specific risk. For the ages 10-19 at the time of exposure this difference in risk tends to reduce to 1.2. In both cases this difference will be expected to decline further as the average age in the cohort increases and the coefficient of risk adopted approaches the coefficient for the whole population. This phenomenon is repeated in the projections for loss of life expectancy.

582. For the additive, rather than the multiplicative, model, the difference between the excess mortalities calculated using the constant coefficient and the age-related coefficient is very small for leukaemia, and it even tends to reverse for the age cohort 10-19. This accords with the fact that the risk coefficient for this particular age group happens to be lower than the average value adopted for computations on the whole population. As is true for the multiplicative model, these effects are almost repeated in the projections for loss of life expectancy.

583. To provide estimates of risk to be applied to the whole population, computations have been made using the various age-at-exposure classes, attributing to each of them the coefficient that applies to that particular class, projecting the risk of that class over the appropriate period of time (40 years or lifetime) and summing up the overall effects over all age-at-exposure classes. This was done for both the multiplicative and the additive projection models and for excess lifetime mortality and loss of life expectancy, separately. The final results of these summations are given in Table 62.

584. Considering the number of fatalities from leukaemia and other malignancies together (upper part of Table 62), it is seen that between about 42 and about 107 deaths would be predicted by the additive and the multiplicative model, respectively. The lower half of the Table shows that between about 950 and 1,370 person-years can be expected to be lost if the whole population is exposed to 1 Gy under the conditions specified.

585. There is a different way of arriving at similar projections; namely, to use a single risk coefficient which does not take age at exposure into account explicitly. It should be noted that this method of projection has its own shortcomings, for a risk coefficient so estimated is essentially a weighted average of the age-specific relative risks with weights proportional to the numbers of cancer deaths in the specific age groups. Thus most of the weight will be given to the older age groups whose actual relative risks are smaller. Nevertheless, to provide a comparison, this has been done in Table 63 in respect to the population of Japan. The values in parentheses provide the corresponding numbers when the upper and lower 90% bounds of the risk estimate are used (see Table 54). It shows that, under the conditions specified above, one would expect to observe a total of about 71 extra fatal cases under the assumption of a multiplicative projection, compared with about 45 cases for an additive projection model.

586. The first method (Table 62) may overestimate the lifetime excess mortality under the multiplicative model as the relative excess risks in the younger age-at-exposure groups has been falling with increasing time since exposure (see Table 51). On the other hand, this method may well underestimate the lifetime excess mortality using the additive model, as the excess risks have been increasing with time since exposure in the younger age-at-exposure groups (see Table 52). Conversely, under the second method (Table 63) the multiplicative model may underestimate the lifetime harm for the younger age-at-exposure groups, but the harm for these groups under the additive model may be overestimated. With the multiplicative risk projection model there is about a 30% decrease in estimated lifetime mortality from all malignancies using the second method compared with the first, while with the additive model the second method leads to about a 50% increase.

3. Extrapolation to other populations

587. Risk coefficients are always estimated, and lifetime risks projected, in the context of a particular population. Each exposed population from which risk coefficients are estimated has its own background mortality rates from all causes of death, and its own age- and sex-specific cancer rates. Indeed, not all individuals within any given population are at the same risk. Considering this, it is fair to ask what use can be made of risk coefficients obtained from one population for predicting lifetime risks in any other population. The projections given in this chapter have been derived by applying the closest possible expected rates of death (from cancer and from all other causes); namely, those from the same country as the exposed. Even so, baseline risks in the Japanese exposed to the atomic bombs, a wartime and post-war environment, were not the same as those of current Japanese, nor even precisely of those of Hiroshima and Nagasaki today. It is known that there are changes occurring in Japan in regard to baseline mortality rates and that there are also regional differences in Japan, as in every other country. Similarly, the all-United Kingdom mortality patterns are certainly not exactly those of the ankylosing spondylitis or the cervical cancer patients.

588. Because baseline mortality is always changing in every population, and this includes major changes in a variety of cancer risk factors, it is difficult to know how accurate lifetime risk projections might be. One way to place outer limits on this error would be to compare the lifetime risk estimates based on the same risk coefficients and different baseline mortality patterns. For this Annex three populations have been chosen to compare projected risks. To do this, the absolute and excess relative risk coefficients derived
from the experiences of the atomic bomb survivors have been applied to (a) the Japanese population using the Japanese 1980 national mortality patterns, representing the nearest available representative rates for the coefficients; (b) the United Kingdom, representing a rather typical older industrialized nation; and (c) Puerto Rico, representing (as best as worldwide data will permit) a population with high infant and infectious disease mortality, and low cancer rates.

589. The populations are compared in Table 64, and the results of this comparison for leukemia, other cancers and all malignancies are given in Tables 65 and 66. The latter Tables show that across these three populations there is virtually no difference in risks projected by the additive model. Even for the multiplicative model, the maximum difference, using Japan as the basis of comparison, is a factor of 71/58 = 1.2. This clearly shows that the lifetime risk projections are very insensitive to differences in overall, and cancer-specific mortality differences within the range of contemporary large national populations, and for leukemia or all cancers pooled. Thus, the risk projections derived here would seem to have rather broad generality and applicability. Much larger proportional differences may apply to site-specific cancer with large international variation in risk, such as female breast, stomach, large bowel and lung.

590. It should be pointed out, however, that this conclusion applies to only one of the uncertainties in the extrapolation of risk projections to other populations. It is not yet known how much the risk coefficients themselves might vary between different ethnic groups or populations with differing exposures to other carcinogens which could act synergistically; the range of today’s knowledge is limited essentially to data from Japan and from a variety of industrialized populations. Within this context, and given the statistical problems in estimation, the range of risk coefficients is rather small, well below a full order of magnitude.

4. Comparisons with previous studies

591. The Committee made its last previous estimates of lifetime risk in the UNSCEAR 1977 Report [U2]. This Report gave values for all cancers of 1.0 \(10^{-2}\) Gy\(^{-1}\) (range 0.75-1.75, Annex G, paragraph 318) for low dose low-LET radiation and 2.5 \(10^{-2}\) Gy\(^{-1}\) (Annex G, paragraph 317) for high dose low-LET radiation. Leukemia was about one fifth of the total. The projection was carried out by assessing the leukemia risk and projecting a ratio of 5-7 for all cancers to leukemia ultimately, thus obtaining the total cancer risk.

592. Additional epidemiological and other information has accumulated since 1977. This includes extensions and changes in the data for the Japanese atomic bomb survivors, in the ankylosing spondylitis series in the United Kingdom and in various other specific tumor sites such as lung (radon), thyroid and breast. A new study of patients surviving treatment for carcinoma of the cervix has provided additional information on second cancers at selected sites. Most of these studies make some contribution to quantitative risk estimates.

593. The atomic bomb survivors are especially important and provide the largest single data set over a range of doses. In this population the data have now accumulated over three additional time periods since the 1977 Report was written, viz. 1975-1978, 1979-1982 and 1983-1985. These are important time periods for the expression of solid tumors, 30-40 years after exposure to the bombs. Not only has the total amount of data on excess cancers increased by approximately threefold, but the extension of the data in time and the increasing information for all age cohorts, especially the young, provide further tests of models and thus aid in methods of projection and in knowledge of age dependence. Furthermore, the dosimetry of the survivors has been evaluated (and measured in the survivor range by thermoluminescent methods) and tends to increase risk by factors, when expressed in terms of shielded kerma, between 1 and 2 depending on the cancer site. Some improvements have also been made in statistical methods.

594. The atomic bomb survivors have been used in this report as the main source of risk estimates, while the Committee notes that other sources of data such as the ankylosing spondylitis patients are in general terms consistent with these estimates, especially when the mode of delivery of the exposure is taken into account. The Committee has not itself made primary estimates of risk in the Japanese atomic bomb survivors, but has relied on risk estimates developed in recent publications for the appropriate period of observation. These risk estimates have then been projected to a lifetime separately by the additive and multiplicative models and for both an age-structured population and for risks averaged over one intermediate age range. Lifetime risks have been estimated separately for an adult population alone and an entire population of all ages.

595. In this Annex the risk estimates for a population of all ages for mortality from all cancers at 1 Gy of high dose rate low-LET radiation range from 4 to 11 \(10^{-2}\) Gy\(^{-1}\) (Table 62), whereas for an adult population alone the range is from 5 to 6 \(10^{-2}\) Gy\(^{-1}\) (Table 59) (the ranges reflecting the additive and multiplicative models of projection, respectively). Leukemia accounts for one quarter to one tenth of the total. The Committee has also provided estimates of the years of life lost as determined by the two projection methods. It may also be noted that while the age dependence has become more evident than in the UNSCEAR 1977 Report, sex differences have become smaller.

596. General appraisals of risk estimates have been made by various other groups since the UNSCEAR 1977 Report. The BEIR III Committee of the National Academy of Sciences in the United States produced a comprehensive report in 1980 [C4] which provided a range of from 0.1 to 5 \(10^{-2}\) Gy\(^{-1}\) for all cancers using additive and multiplicative models for projection and quadratic, linear-quadratic and linear models for dose response. The preferred values of risk at the time the
report was issued were based on the linear-quadratic model and on additive projection and were quite similar to the values in the UNSCEAR 1977 Report (see [C4], Table V-25).

597. Later, for a report of the Nuclear Regulatory Commission in the United States, Gilbert [G11] developed risk estimates based on a linear-quadratic dose-response model (together with upper and lower bounds, roughly a factor of 3 above and below) and both additive and multiplicative projection models and years of life lost (Tables 8 and 9). The lifetime risk estimates ranged from about 0.3 to 6 $10^{-5}$ Gy$^{-1}$ with a central value of about $2.10^{-2}$ Gy$^{-1}$ for low doses of low-LET radiation.

598. A group constituted by the National Institutes of Health in the United States assembled risk information for the purpose of developing tables of probability of causation (i.e., risk estimates for specific cancer sites at nominal ages as a function of time after exposure [U33]). The input used risk information updated from the BEIR III report similar to that of Gilbert. Lifetime risk estimates can be derived from the basic input using an additive projection model and again values of about $2.10^{-2}$ Gy$^{-1}$ for low doses would be found.

599. These two recent groups had access to data from the Japanese atomic bomb survivors up to 1978 but were too early to obtain the full benefit of recent risk estimates from Japan utilizing the additional time periods and revised dosimetry now available to this Committee and included in this analysis.

D. RISKS AT LOW DOSES AND LOW DOSE RATES

600. At doses and dose rates defined by the Committee as low (less than 0.2 Gy and less than 0.05 mGy/min for low-LET radiation) radiation-related carcinogenic effects in an exposed population will almost always be masked by the larger carcinogenic effects of other factors. Moreover, in an exposed study population there will always be some level of dose below which no statistically significant excess of cancer occurs compared with the control population. In the dose range below this point, the excess cancer risk cannot be observed and cannot therefore be directly determined. In this dose range the Committee has to use a model to interpolate between the certainly zero excess risk at zero dose and the observed excess risk at doses of the order of 1 Gy. This may require the use of a correction factor if the projections based on high doses and high dose rates are to be applicable to exposures to low doses and low dose rates.

601. In the risk estimates derived above, no correction was made for the possible reduction of effects under conditions of low dose or low dose rate. The experimental literature contains a wealth of data showing that there are such effects. This has been recently reviewed by UNSCEAR [U1] and earlier by the National Council on Radiation Protection [N1]. The former report concludes that for low-LET radia-

tion most dose-response curves for tumours induced in animals are concave upward and may be fitted by linear-quadratic or quadratic models, although in some cases linearity may apply. Moreover, dose rate studies with low-LET radiation almost invariably show a decreased incidence of tumours with decreasing dose rate in animal populations.

602. The human data on this subject are sparse, but are reviewed in the UNSCEAR 1986 Report [U1] which concludes that extrapolation linearly down to zero dose would overestimate the risk by a factor up to 5 in typical situations. The study by Howe [H6] and the very recent study by Holm [H28] are not considered in the UNSCEAR 1986 Report but are discussed earlier in the present Annex.

603. Since 1986 new data on human populations relevant to the effects of low doses have emerged from the revision of the experience in atomic bomb survivors [S49]. Table 67 shows the excess relative risk per 1 Gy of organ absorbed dose for doses above and below 0.5 Gy, using the entire 0-6 Gy dose range, and for progressively lower dose ranges below 1 Gy [S49]. Considering first leukaemia, a significant difference in the excess relative risk exists among survivors exposed to 0.5 Gy or more, as opposed to those exposed to lower doses (5.53 versus 2.44, respectively). This suggests persistence of a curvilinear dose-effect relationship for haematopoietic malignancies. In so far as all cancers except leukaemia are concerned, the excess relative risk associated with the higher doses does not differ significantly from that at the lower doses (0.41 versus 0.37, respectively). At doses below 0.20 Gy, the Japanese data have not revealed a significant excess of malignant tumours, and the nature of the dose-response relationship at these doses is uncertain. The expected numbers of additional cancer deaths at these lower doses are still small, relative to the background rate, even under the linear dose-response model, and the scatter of the data points is such that they can be fitted almost equally well by a quadratic, linear-quadratic or linear dose-response relationship [S48].

604. Epidemiologic studies of continuous internal irradiation of the thyroid gland by $^{131}$I represent one source of information on the effect of low dose rates in human populations. A preliminary study of 10,000 patients who received doses to the thyroid gland in the range of 0.5 to 1.5 Gy found no excess of thyroid cancer after a mean follow-up of 17 years although 16 excess cases would have been expected based on external low-LET irradiation of the thyroid [H27]. An analysis of this study by the National Council on Radiation Protection of the United States concluded that $^{131}$I should be considered no more than one-third as effective as external irradiation at high dose rates probably due to factors related to dose rate and dose distribution. An expanded study of 35,000 patients receiving diagnostic examinations has been published [H28]. These studies are discussed in paragraph 398. Both conclude that doses received from internal $^{131}$I irradiation are less carcinogenic than similar doses from external acute irradiation. A factor of at least 3 has been proposed [N5], and possibly even 4 [H26]. Although the reduction of dose rate is held by some to
be a major contributor to the evident reduction in effectiveness. Others contend that non-uniformity of dose distribution in the gland from $^{131}I$ may occur and contribute too [N5].

605. Epidemiologic studies of highly fractionated exposures to external low-LET radiation represent a second source of information on a low dose or low-dose rate factor. As discussed in paragraph 367, there appears to be a non-linear dose response in the Canadian study of breast cancer following multiple fluoroscopic examinations [H6]. This appears to be related to the much smaller dose per examination received by the breasts of women who were irradiated posteriorly rather than anteriorly. A fractionation effect was not demonstrated in the similar but much smaller Massachusetts study [B3]. However, in this study it was not possible to distinguish a low dose cohort irradiated posteriorly. There appears to be a low dose or low dose rate factor of at least 3 in the Canadian study [H6].

606. Previous attempts to estimate lifetime risk for humans, such as BEIR III [C4], the Nuclear Regulatory Commission [G11], and the National Institutes of Health [U3] have handled the problem posed by low doses and low dose rates differently. BEIR III used a linear-quadratic dose-response function as one of their tested models, but the BEIR III Committee felt unable to recommend a specific general reduction for low dose rates. The other reports [G11, U3] both relied on the NCRP summary of the experimental literature [N1]. This was done by using a quadratic term in the dose-response function only for modelling exposure at low-dose rates. In the central estimates by Gilbert [G11], for which the results are given in Table 8, the linear coefficient was reduced by a factor of 3.3, and in the lower bound estimates by a factor of 10, for all organs except breast and thyroid.

607. From examination of both experimental and human data the Committee concludes that the carcinogenic effects of low-LET radiation are generally smaller at low doses and at low dose rates compared with those at high doses and dose rates. The reduction factors will vary with dose and dose rate and with organ system but will generally fall within the range 2 to 10.

### E. LIFETIME RISK ESTIMATES FOR SPECIAL TISSUES

#### 1. Lung

608. The computations provided in this Annex, based on DS86 risk coefficients, include low-LET, high-dose-rate exposure to the lung, based on the atomic bomb survivor experience. However, it is important to also estimate risk coefficients and lifetime risks for the alpha-irradiation experienced in connection with radon daughter exposure in the home and workplace. Thomas et al. [T20], ICRP [I11], and BEIR IV [C20] have reviewed the literature on radon (and related) exposures and have estimated lifetime risk. The Committee has reviewed these findings, along with other recent reports, in chapters III and IV.

609. Life-table methods essentially identical to those used in this Annex have been used by ICRP [I11] to derive lifetime risk estimates for continuous exposure to radon progeny, the high-LET exposure. Since the Committee believes that these estimates are reasonable in the light of the available data, it simply presents them in Table 68.

610. Thomas et al. [T20] have provided risk estimates for two types of exposure: (a) occupational exposure at 4 WLM up to a maximum of 200 WLM and (b) lifetime exposure of 0.02 WL 17 hours per day, 7 days per week as an upper tolerable limit for exposure that might be experienced in homes. The risk figures were adjusted for active breathing (occupational exposure) and quiescent breathing (home exposure), but they were not adjusted for age to account for varying susceptibility. The authors suggest, however, that since recent dosimetric studies indicate that breathing rate corrections may be inappropriate, their lifetime natural risk estimates might be doubled. Thomas et al. [T20] used eight risk models; namely, all combinations of additive and multiplicative projections: constant and age-varying risk coefficients; exposure times over which exposure is effective in incrementing risk. The projections were based on the Canadian life-table and lung cancer risks. Table 10 provides their risk coefficients and the lifetime excess risks.

611. The ICRP used similar assumptions and essentially the same demographic method of projection [I11]. Their publication reviews the entire literature, biological and physical, on radon daughter exposure, including the available studies on mining, in-home exposures and the relationship of risk to smoking, age, sex, and latency period. Their results are given in Table 68. For details and the methods of deriving the risk coefficients see the ICRP study [I11]. The ICRP concludes that the multiplicative risk projection model gives a better "best" fit for the data and provides a more realistic way of extrapolating from the higher mining doses to lower in-home doses than the additive model. It cites several published estimates, ranging from 0.10% to 1.0% excess cases at a constant annual exposure of 0.19 WLM.

612. Risk estimates for adult male uranium miners have been reviewed in [C20, I11, I12, U2]. More recent publications and papers prepared for publication have been noted by the Secretariat. Some of these data suggest that the minimum latency period to initial appearance of excess lung cancers after first exposure to high concentrations of radon progeny is five years, rather than the 10 years previously assumed [K28, M40, S51]. The interaction between cigarette smoking and exposure to radon progeny was closer to additive than to multiplicative for the Czech miners [S51]. These data have not yet been analysed in depth by the Committee. The preliminary analysis available does not suggest any reason for a major change in the previous risk estimates [I12, U2] of 1.5-4.5 $10^{-4}$ fatal lung cancers per WLM. More detailed consideration of epidemiological data relating to lifetime risk estimates for cancer induction by inhalation of radon and radon progeny is anticipated in future UNSCEAR Reports.
2. Bone

613. The Committee is unable to provide reasonable lifetime risk estimates for exposure to low- or high-LET irradiation for bone cancer. The data from Japan do not provide statistically meaningful risk coefficients, and there are problems with using the available literature on adults (e.g., the radium dial painters and patients injected with radium isotopes) to assess lifetime risk with demographic projection methods. The literature is summarized in chapter III.

614. While exposed children are probably sensitive to bone cancer induction, the genetically atypical nature of the available cohorts, relative to whole-body exposure, precludes a useful estimation of risk from their data, other than as discussed in chapter III.

3. Thyroid

615. The best estimates of thyroid cancer are available from [N5], and were given in Table 39. This was based on the most recent data yet available. There are no published data from Japan from which to make projections beyond those already given in this Table. Recent data from Holm [H28] have been noted earlier.

F. RISK ASSESSMENT BY CANCER TYPE

616. In section VII.C, the Committee calculates the projected risk of induction of malignancies for two broad classes of malignancy: leukaemia and other solid cancers. The reason for considering only these two classes is that in the patient series reported there are not enough observations to allow separate computations for all cancer sites and all ages in order to obtain an overall estimate. The only series in which there appears to be enough information for at least an exploratory site-specific analysis is that on the atomic bomb survivors from Hiroshima and Nagasaki. Therefore, simply to show what type of data the model used could generate—given the appropriate background information—the Committee has refined its analysis of the Japanese series to compute the risk of radiation-induced cancers by anatomical site, on the basis of multiplicative and additive risk projection models and for the two indices of radiation harm described earlier. These computations were performed using the risk coefficients and the assumptions specified in Tables 56 and 57; the results are given in Tables 69 and 70.

617. It should be borne in mind that the final results of the computations are no better than the original data from which they were derived. Although the atomic bomb survivor study is the only study that allows these projections, the number of cancers observed for each site and each age class is often small. Consequently, the projected values carry large uncertainties. It should also be pointed out that these computations apply strictly to the Japanese population and could not be transferred easily to other populations having different demographic and epidemiological characteristics.

618. The Tables are computed on the assumption of an age-constant risk coefficient, since there was not enough information for most sites (particularly in young cohorts) to allow meaningful analysis of the radiosusceptibility of young cohorts exposed below 20 years of age separately for each site. Taking this factor into account would, of course, increase the risk attributable to younger ages and, since these ages dominate the overall risk projection, they would increase the expected risk substantially. The Committee considers that taking an average risk coefficient overestimates to some extent the risk of the age classes that are old at the time of exposure and underestimates the risk of the younger cohorts. The data available at present do not allow quantification of this statement on a site-by-site basis.

619. Table 69 presents the expected additional cancer cases at nine specific sites, including the marrow, and for all other sites collectively, designated as the remainder, under the two risk projection models. It should be noted that the number of excess cancers at sites not specifically identified, i.e., the remainder, has been computed. first, through subtraction of the excess cancers at the identified sites from the total projected excess number at all sites and, second, through the actual computation of the risk coefficient associated with this collection of sites, and projecting the excess number from the estimated risk coefficient. The difference between these two methods of estimating the expected number is small. Table 70 summarizes the loss of life expectancy per person after exposure to 1 Gy, under the same assumptions as in Table 69.

G. SUMMARY AND CONCLUSIONS

620. The Committee had available to it certain additional data that made it desirable to reconsider the assessment of the risk of radiation-induced cancer. These additional data were the result of: (a) a re-evaluation of the doses of the Japanese atomic bomb survivors; (b) an extension of the observation periods for several cohorts during which radiation-induced cancers continued to occur; (c) the availability of data from several new cohorts; and (d) the introduction into the analysis of both the additive and the multiplicative risk projection models for lifetime cancers and loss of life expectancy, taking into account competing causes of mortality.

621. In its projections, summarized in Table 71, some of the risk coefficients used by the Committee were derived by the authors of the reports from which they were taken using a linear dose-response relationship. However, there is no direct epidemiological evidence that substantiates this at low doses and/or low dose rates, and there is in addition some epidemiological evidence of non-linearity. Based primarily on the experience of the atomic bomb survivors who received uniform whole-body irradiation at high doses and dose rates and low-LET, the Committee derived excess absolute and relative risk coefficients. Using these risk coefficients, the Committee estimated lifetime risks of mortality in the range of 4 to 11 × 10⁻² Gy⁻¹. The Committee considered that these risk estimates apply to a dose range of 0.5-6 Gy and noted that they are
strongly influenced by the finding that children are considerably more sensitive to radiation effects than adults.

622. The above estimates are qualified by the facts that (a) the estimates have been derived using Japanese data and the extent to which they apply to other populations is not clear; (b) although the multiplicative model leads to higher estimates of projected mortality than the additive model, the projected estimates of the expected years of life lost are similar under the two models. This is because under the multiplicative model a large proportion of the projected deaths occur in very old people when the years of life lost are few; and (c) there are two other major cohorts, those of patients irradiated for ankylosing spondylitis and cervical cancer, which give rise to somewhat lower estimates of lifetime risk.

623. The Committee agreed that there was a need for a correction factor to modify the risks given above for low doses and low dose rates. The Committee considered that such a factor certainly varies widely with individual tumour type and with dose rate. However, the appropriate value to be applied to total risk for low dose and low dose rate should lie between 2 and 10. The Committee intends to study this matter in detail in the future.

624. The Committee has not presented risk estimates for high-LET radiation in general in this Annex except for the exposure to radon of uranium miners. For low doses of external high-LET radiation it would be necessary to multiply the risks for low-LET radiation by an appropriate quality factor. No dose or dose rate reduction factor is considered necessary for high-LET radiation at low doses.