2. Studies of Cancer in Humans

Knowledge of the carcinogenic effects of internally incorporated radionuclides in humans is derived principally from observational studies of individuals exposed to unusual amounts of radiation, either occupationally, environmentally or medically. The most common study design is that of the cohort study, in which a group of individuals is defined by their employment, by the fact that they have received a certain medical treatment or procedure or by residence in a certain area at a certain time. The group of individuals is then followed forward in time, and the rate at which they develop, or die from, specific types of cancer is documented and compared with the rate that would be expected in the absence of any unusual radionuclide exposure, as defined by the rates in an appropriate external comparison population. Alternatively, internal comparisons can be made between groups of individuals defined and followed forward by the investigator but exposed to radionuclides at a different level, allowing in the most favourable circumstances the construction of a dose–response relationship. In addition to cohort studies, there are a few studies of the case–control design in which individuals who have already developed a certain type of cancer are identified, together with other individuals who are representative of the population from which the individuals with cancer have been drawn, and the past exposure of diseased and non-diseased individuals is compared.

The interpretation of observational studies in this field is often difficult, as the exposed and unexposed groups may differ in ways other than simply their radionuclide exposure. In the ideal situation, information on all likely confounding factors, including age, sex, smoking history and exposure to external radiation would be available, thus enabling their effects to be disentangled from that of the radionuclide. In practice, the circumstances of exposure usually preclude an ideal study design. Nevertheless, humans have been exposed to radionuclides in a wide variety of circumstances, and, as summarized in the following sections, it has in many cases proved possible to characterize the effects of exposure.

2.1 Radon

Radon is a noble gas occurring in several isotopic forms. Only two of these are found in significant concentrations in the human environment: ^{222}Rn and ^{220}Rn (thoron). The major radioactive exposure of public health concern is inhalation of short-lived decay products (^{218}Po and ^{214}Po) of ^{222}Rn (called radon in this section). Underground miners of

uranium and other depositions in igneous rocks have often been exposed to substantial concentrations of radon. Radon is also the most important source of ionizing radiation of the populations of most countries (see section 1). The effects of exposure to radon have been reviewed previously (IARC, 1988; Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). With its decay products, it was classified by IARC in Group 1 (carcinogenic to humans). The effects of exposure to ^{220}Rn are discussed in the section on thorium.

2.1.1 *Occupational exposure in underground mining*

In 1987, when the carcinogenicity of radon was first evaluated by an IARC Working Group, eight cohort studies of underground miners exposed to high concentrations of radon gas had been published (IARC, 1988). Since then, additional data have become available for most of these studies, and the results of four additional studies have been published; one study of some 60 000 workers with 1500 lung cancers is still in progress (Kreuzer *et al.*, 1999) and the results are not yet available. These studies are described here briefly and are summarized in Tables 33 and 34.

(*a*) *Lung cancer*

(i) *Mining*

The original references for the reports of these studies are given in Tables 33 and 34. The data from all studies except that carried out in Cornwall, United Kingdom, were compiled by Lubin *et al.* (1995a) and the Committee on Health Risks of Exposure to Radon (BEIR VI) (1999).

The Yunnan (China) cohort study consists of more than 17 000 employees of the Yunnan Tin Corporation in southern China, assembled from an occupational survey in 1976 (BEIR VI). Vital status was determined from occupational and retirement records, and lung cancer deaths were ascertained from a Corporation-operated cancer registry; ascertainment is thought to be complete. Follow-up was performed until 1987. A substantial number of the miners were under the age of 20 at the start of exposure. Data on tobacco use were available for 76% of the cohort but only after 1976; the information on duration and amount of smoking is incomplete. Of the exposed persons, 936 died from lung cancer; 44 lung cancer deaths were found in the unexposed cohort, yielding an excess relative risk (ERR)/WLM of 0.0016 (95% confidence interval [CI], 0.001–0.002) (Lubin *et al.*, 1995a). High concentrations of arsenic were also present in the mine and were associated with the risk for lung cancer.

A cohort study of uranium miners in western Bohemia, Czech Republic, comprised 4320 exposed and 656 unexposed workers (BEIR VI). The main analysis was performed on data for miners who started working in 1948–57. Vital status and disease outcome were obtained from a population registry. The follow-up period covered 1952–90, yielding an average follow-up period of 25.2 years. No data on smoking were available. Among the exposed men, 656 (Lubin *et al.*, 1995a) [701 (BEIR VI)] died

Table 33. Exposure in cohort studies of underground miners occupationally exposed to radon

Study (references)	Type of mine	Person–years		WLM[a]	No. of years exposed[a]
		Exposed	Unexposed		
Yunnan, China (Qiao *et al*., 1989; Xuan *et al*., 1993; Yao *et al*., 1994)	Tin	135 357	39 985	277.4	12.9
Western Bohemia, Czech Republic (Ševc *et al*., 1988, 1993; Tomášek *et al*., 1993, 1994a,b; Tomášek & Darby, 1995; Tomášek & Placek, 1999)	Uranium	103 652	4 216	198.7	7.3
Colorado, USA[b] (Hornung & Meinhardt, 1987; Roscoe *et al*., 1989; Moolgavkar *et al*., 1993; Thomas *et al*., 1994; Roscoe *et al*., 1995; Roscoe, 1997; Hornung *et al*., 1998; Luebeck *et al*., 1999; Stram *et al*., 1999a,b)	Uranium	73 509	7 403	595.7	4.0
Ontario, Canada[c] (Müller & Kusiak, 1989; Kusiak *et al*., 1993)	Uranium	319 701	61 017	30.8	3.0
Newfoundland, Canada (Morrison *et al*., 1988, 1998)	Fluorspar	35 029	13 713	367.3	4.8
Malmberget, Sweden (Radford & St Clair Renard, 1984)	Iron	32 452	841	80.6	17.8
New Mexico, USA (Samet *et al*., 1989, 1991, 1994)	Uranium	46 797	12 152	110.3	7.4
Beaverlodge, Canada (Howe *et al*., 1986; L'Abbé *et al*., 1991; Howe & Stager, 1996; Chambers *et al*., 1999)	Uranium	68 040	50 345	17.2	1.9
Port Radium, Canada (Howe *et al*., 1987)	Uranium	30 454	22 222	242.8	3.2
Radium Hill, Australia (Woodward *et al*., 1991)	Uranium	25 549	26 301	7.6	1.1
France (Tirmarche *et al*., 1993)	Uranium	39 487	4 556	68.7	13.2
All above combined[d] (Lubin *et al*., 1995a)		907 459	242 332	158.0	5.7
Cornwall, United Kingdom (Hodgson & Jones, 1990)	Tin	[2 535]	NR	[65]	[11]

WLM, working-level months; NR, not reported

[a] Means for radon-exposed miners

[b] Totals exclude values > 3200 WLM, including those for 35 lung cancer cases.

[c] Values are given for all uranium miners, including those with previous gold-mining experience.

[d] The data from the original papers, except the study in Cornwall, United Kingdom, were compiled by Lubin *et al.* (1995a). Totals adjusted for 115 workers (including 12 lung cancer patients) who were included in both the New Mexico and Colorado cohorts.

Table 34. Relative risks in cohort studies of underground miners occupationally exposed to radon

Study (references)	Type of mine	Lung cancer deaths		ERR/WLM[a]	95% CI
		Exposed	Unexposed		
Yunnan, China (Xuan *et al*., 1993)	Tin	936	44	0.0016	0.001–0.002
Western Bohemia, Czech Republic (Tomášek *et al*., 1994a)	Uranium	656	5	0.0034	0.002–0.006
Colorado, USA[b] (Hornung & Meinhardt, 1987)	Uranium	292	2	0.0042	0.003–0.007
Ontario, Canada[c] (Kusiak *et al*., 1993)	Uranium	282	2	0.0089	0.005–0.015
Newfoundland, Canada (Morrison *et al*., 1988)	Fluorspar	112	6	0.0076	0.004–0.013
Malmberget, Sweden (Radford & St Clair Renard, 1984)	Iron	79	0	0.0095	0.001–0.041
New Mexico, USA (Samet *et al*., 1991)	Uranium	68	1	0.0172	0.006–0.067
Beaverlodge, Canada (Howe *et al*., 1986)	Uranium	56	9	0.0221	0.009–0.056
Port Radium, Canada (Howe *et al*., 1987)	Uranium	39	18	0.0019	0.001–0.006
Radium Hill, Australia (Woodward *et al*., 1991)	Uranium	32	22	0.0506	0.010–0.122
France (Tirmarche *et al*., 1993)	Uranium	45	0	0.0036	0.001–0.013
All above combined[d] (Lubin *et al*., 1995a)		2 597	109	0.0049	0.002–1.010[e]

ERR/WLM, excess relative risk per working-level month; CI, confidence interval

[a] Means for radon-exposed miners

[b] Totals exclude values > 3200 WLM, including those for 35 lung cancer cases.

[c] Values are given for all uranium miners, including those with previous gold-mining experience.

[d] The data from the original papers were compiled by Lubin *et al*. (1995a). Totals adjusted for 115 workers (including 12 lung cancer patients) who were included in both the New Mexico and Colorado cohorts.

[e] Joint 95% CI based on random effects model

from lung cancer, while there were only five lung cancer deaths in the unexposed cohort, yielding an ERR/WLM of 0.0034 (95% CI, 0.002–0.006) (Lubin *et al.*, 1995a).

The study of Colorado (USA) uranium miners is one of the earliest cohort studies, the first results having been published in the 1960s (Archer *et al.*, 1962; Wagoner *et al.*, 1964, 1965). The cohort consists of 3347 exposed workers in Arizona, Colorado, New Mexico and Utah who had completed at least one month of underground mining and who had had at least one (voluntary) medical examination (BEIR VI). Vital status was ascertained from company records, the State vital statistics office, the National Death Index and by direct contact. The cause of death was determined from State death certificates. Data on smoking for 1950–60 and 1963–69 were obtained from annual censuses and from mailed questionnaires. Among the exposed men, 292 died of lung cancer, while only two lung cancer deaths were observed among the unexposed members of the cohort. The ERR/WLM is 0.0042 (95% CI, 0.003–0.007). The cumulative exposure to radon was among the highest seen in studies of miners (Lubin *et al.*, 1995a).

The cohort study of Ontario, Canada, uranium miners (BEIR VI) covered persons who had had an obligatory medical examination between 1955 and 1984 and who had been employed for a minimum of five years in dusty jobs or for a minimum of two weeks in mining. Vital status and cause of death were determined for 1955–86 through the mortality database of Canada. The cohort consisted of 21 346 exposed male miners with an average duration of exposure of three years and an average length of follow up of 17.8 years. Data on smoking were available from several surveys, and after 1976 smoking history was recorded annually. In the exposed cohort, 282 (Lubin *et al.*, 1995a) [285 (BEIR VI)] men died from lung cancer. Two persons in the unexposed cohort died from lung cancer, yielding an estimated ERR/WLM of 0.0089 (95% CI, 0.005–0.015).

The cohort of Newfoundland, Canada, fluorspar miners comprised men who had worked in one of two local mining companies between 1933 and 1978 and for whom adequate personal identification was available (BEIR VI). Vital status and cause of death were determined for the years 1950–84 from the Mortality Database of Statistics, Canada. Information on smoking was obtained from several surveys but was available for only 48% of the cohort. The average duration of exposure was 4.8 years, and the average follow-up was 23.3 years. The cohort comprised 1751 exposed miners, among whom 112 deaths from lung cancer were observed; as six lung cancer deaths were found in unexposed men, the ERR/WLM was 0.0076 (95% CI, 0.004–0.013) (Lubin *et al.*, 1995a).

The Swedish cohort study covered men who had worked in iron mining in the Malmberget area in the northern part of Sweden (BEIR VI). Men born between 1880 and 1919 and still alive in 1930 and who had worked for more than one year in mining between 1897–1976 were included in the study. Vital status and cause of death were determined for the period 1951–91, and the information is thought to be complete owing to the Swedish system of personal identification numbers. Information on

smoking was obtained from several surveys and was available for all men who had died from lung cancer and for more than half of the men still alive in 1970. The cohort comprised 1294 exposed miners with an average duration of exposure of 18.2 years and an average follow-up of 25.7 years. Of the exposed men, 79 died from lung cancer. The ERR/WLM is 0.0095 (95% CI, 0.001–0.041) (Lubin *et al.*, 1995a).

The New Mexico (USA) cohort represents the most recently employed miners in the USA. Men who had worked for at least one year underground in New Mexico before December 1976 were included in the study (BEIR VI). Vital status was determined from various sources, including the New Mexico vital statistics records and the National Death Index. Death certificates were obtained and causes of death coded by one nosologist. A total of 3457 exposed miners were included in the study, with an average of 5.6 years' exposure and 17 years' follow-up. The follow-up covered the period 1943–85. Medical records were available to categorize the miners into current smokers, former smokers and non-smokers. In total, 68 exposed and unexposed miners died from lung cancer, yielding an ERR/WLM of 0.0172 (95% CI, 0.006–0.067) (Lubin *et al.*, 1995a).

The Beaverlodge uranium mine in Canada began operation in 1949 and was closed in 1982. The cohort study included men who had ever worked at the uranium mine during 1948–80 (BEIR VI). Vital status and causes of death were determined for 1950–80 by searching the Mortality Database of Statistics, Canada. In total, 6895 miners were enrolled in the study, with an average duration of exposure of 1.7 years and an average period of follow-up of 14 years. No information on smoking was available for the members of the cohort. Fifty-six lung cancer deaths were observed in the exposed group and nine in the unexposed, for an ERR/WLM of 0.022 (95% CI, 0.009–0.056) (Lubin *et al.*, 1995a).

The Port Radium, Canada, cohort consisted of 1420 men who had worked in a uranium mine since 1940 and who were known to be alive on 1 January 1945 (BEIR VI). Vital status and cause of death for the period 1950–80 were obtained by searching the Mortality Database of Statistics, Canada. The average duration of exposure was 1.2 years, and the average follow-up was 25.3 years. No data were available on smoking. Overall, 39 lung cancer deaths were observed in the exposed cohort and 18 in the unexposed, giving an ERR/WLM of 0.0019 (95% CI, 0.001–0.006) (Lubin *et al.*, 1995a).

The Radium Hill cohort studies covered 1457 exposed hourly workers who had been employed at the Radium Hill uranium mine in South Australia during 1952–61 (BEIR VI). Vital status was determined from death records for Australia for the period 1960–87; for years prior to 1960, the search was restricted to South Australia. The average duration of exposure was 1.1 years, and the average length of follow-up was 21.9 years. Data on smoking (ever/never) were available for about half of the cohort from a survey carried out in 1984 among cohort members and their next-of-kin. The total numbers of lung cancer deaths were 31 among the exposed men and 22 among unexposed men (ERR/WLM, 0.051; 95% CI, 0.01–0.12) (Lubin *et al.*, 1995a).

The French cohort included uranium miners from three areas in the centre of France and one area on the west coast (BEIR VI). Men who had worked for at least

two years and who had started work between 1946 and 1972 were included in the study. A total of 1769 exposed men were enrolled who had an average duration of exposure of 7.2 years and an average length of follow-up of 24.7 years. Vital status was ascertained from several sources, including company and national records. Causes of death were obtained for 96% of the deceased persons. No data on smoking were available. In the exposed cohort, 45 men died from lung cancer (ERR/WLM, 0.0036; 95% CI, 0.001–0.013) (Lubin *et al.*, 1995a).

A cohort study of tin miners in Cornwall (United Kingdom) comprised 3010 men, of whom 2059 had worked underground (Hodgson & Jones, 1990). Workers had to have been employed for at least one year between 1941 and 1984. Follow-up was performed until the end of 1986 from the records of the United Kingdom National Health system and was successful for 97.6% of the cohort. No data on smoking were used in the analysis. The observed numbers of deaths were compared with those expected on the basis of national death rates. There was a significant increase in the rate of death from lung cancer (standardized mortality ratio [SMR], 1.58 ($p < 0.05$), based on 105 observed cases, 66.6 expected). The rate increased significantly with increasing exposure ($p < 0.001$).

All the studies summarized by Lubin *et al.* (1994a, 1995a) and shown in Tables 33 and 34 found clear evidence of an increasing risk for lung cancer associated with increasing cumulative exposure to radon. In a pooled analysis of the data from these 11 studies, radon-exposed miners with a cumulative exposure of < 50 WLM had 453 604 person–years at risk, and 353 died from lung cancer (Lubin *et al.*, 1997). A separate analysis of 274 161 person–years at risk and 115 lung cancer deaths among unexposed miners showed a significant association between exposure to radon and the risk for lung cancer. The ERR was 0.012/WLM with a 95% CI of 0.002–0.025.

(ii) *Inverse dose-rate effect*

An inverse dose-rate effect is a phenomenon whereby, for a given dose or cumulative exposure, the probability of a cancer being caused per unit dose received increases as the dose-rate is lowered. An inverse dose-rate effect was first reported in analyses of uranium miners on the Colorado Plateau and in western Bohemia, Czech Republic (Hornung & Meinhardt, 1987; Ševc *et al.*, 1988) and was confirmed in more recent publications on these studies (Tomášek & Darby, 1995; Hornung *et al.*, 1998). A similar effect was reported for Chinese tin miners (Xuan *et al.*, 1993). A comparison of published risk estimates from various studies also showed an inverse dose-rate effect (Darby & Doll, 1990). A joint analysis of data on 11 cohorts of miners showed a significant inverse dose-rate effect in all but one of the studies (Lubin *et al.*, 1995b; Table 35). This analysis also showed no inverse dose–rate effect at total cumulative exposures of < 50 WLM. The phenomenon at very high doses is related in part to cell killing. As the lowest concentrations might be experienced in residential settings, the effect is not apparently consistent with biophysical understanding (Brenner, 1994).

Table 35. Numbers of lung cancer cases, estimates of excess relative risk (ERR) per working-level month (WLM) and its modification by continuous exposure rate in working level (WL)

Study cohort	Cases of lung cancer[a]	$\beta \times 100$	γ	p[b]
Yunnan, China	980	0.59	–0.79	< 0.001
Former Czechoslovakia	661	5.84	–0.78	< 0.001
Colorado, USA	294	14.50	–0.79	< 0.001
Ontario, Canada	291	2.40	–0.55	0.002
Newfoundland, Canada	118	5.14	–0.53	< 0.001
Malberget, Sweden	79	1.55	–1.02	0.03
New Mexico, USA	69	6.56	–0.30	0.17
Beaverlodge, Canada	65	7.42	–0.67	0.001
Port Radium, Canada	57	1.15	–0.42	0.24
Radium Hill, Australia	54	5.68	–0.63	0.30
France	45	1.92	0.57	0.57

From Lubin *et al*. (1995b). Background lung cancer rates are adjusted for attained age (all studies), other mine exposures (China, Colorado (USA), Ontario (Canada), New Mexico (USA), France) and indicators of exposure to radon progeny (Beaverlodge, Canada), and ethnicity (New Mexico, USA). In the studies in Colorado, only exposure to < 3200 WLM was considered. The relative risk (RR) is modelled by the form $RR = 1 + \beta \times WLM \times (WL)^{\gamma}$.

[a] Total number of cases is 2701, omitting 12 cases included in both the New Mexico and Colorado studies.

[b] p for test of significance of continuous variation of ERR/WLM by WL (i.e. test of $\gamma = 0$)

(iii) *Effect in lifelong non-smokers*

As a large proportion of the underground miners studied were cigarette smokers, questions have arisen about whether the association between radon and lung cancer seen in the miners is due to confounding by smoking, or whether radon acts as a lung carcinogen only in smokers. A study of Colorado uranium miners who had never smoked (Roscoe *et al.*, 1989), including 14 who had died from lung cancer, showed a highly significant, 13-fold greater risk compared with that of veterans in the USA who had never smoked. Several other studies have also included non-smokers or light smokers and found an increased risk associated with exposure to radon (Radford & St Clair Renard, 1984; Samet *et al.*, 1991a). Further information is available from the pooled analysis of 11 miner cohorts (Lubin *et al.*, 1995a), in which 2798 workers were reported to be lifelong non-smokers. These data cover 50 493 person–years of follow-up and 64 lung cancer cases. The relative risks increased significantly with increasing WLM for both smokers and lifelong non-smokers. The estimated ERR/WLM for the latter was 0.010 (95% CI, 0.002–0.057), just over three times the corresponding value

for smokers. In interpreting this finding, it must be recalled that the baseline rate of lung cancer is lower among non-smokers, so that the absolute risks of non-smokers are lower than those of smokers.

(iv) *Exposure of women and children*

There were virtually no female workers in the mining populations studied, and the exposure of the vast majority of the miners did not start until adulthood. The one exception is the study of Chinese tin miners, in which a substantial proportion of the workforce was aged under 20 at the start of exposure (Yao *et al*., 1994). The data from this study have been analysed by subdividing the group by age at first exposure (Table 36). No significant variation in the ERR/WLM was found.

Table 36. Excess relative risk (ERR) for lung cancer per working-level month (WLM) and its variation with age at first exposure in the study of tin miners in Yunnan, China

Age at first exposure (years)	Cases	Controls	ERR/WLM (%)	p[a]
< 10	35	28	0.38	0.58
10–14	167	185	0.30	
15–19	82	115	0.25	
20–24	38	73	0.18	
≥ 25	59	167	0.30	

From Yao *et al*. (1994). All models were stratified by smoking status, age, source of subject (Gejiu City or Yunnan Tin Corporation) and type of respondent (individual or surrogate).

[a] p for test of homogeneity of ERR/WLM over categories of age at first exposure

(*b*) *Cancers other than lung cancer*

Information on mortality from cancers other than lung cancer was published for some of the cohorts of underground miners exposed to radon (Waxweiler *et al*., 1983; Morrison *et al*., 1988; Tirmarche *et al*., 1993; Tomášek *et al*., 1994b; Darby *et al*., 1995a,b), but for many it was not. Some excesses were reported, but there was no consistent pattern to the findings, and in most cases the small numbers of deaths limited exposure–response analysis and interpretation. The data from the studies of miners were brought together systematically in a pooled analysis of 11 of the 12 studies of miners listed in Table 33 (Darby *et al*., 1995b). The Radium Hill study (Australia) was omitted because follow-up was incomplete for cancers other than of the lung. In addition, the Yunnan cohort could not be included in comparisons of the numbers of deaths observed compared with those expected from regional or national rates because appropriate external rates were not available. However, this study was

included in internal comparisons of the association between specific cancers and cumulative exposure to radon. Except in China, the mortality rate from all cancers other than lung cancer was close to that expected from rates in the areas surrounding the mines (ratio of observed to expected deaths, 1.01; 95% CI, 0.95–1.07, based on 1179 deaths) and did not increase with increasing cumulative exposure. Among 28 individual cancer categories, statistically significant increases in mortality were found for cancers of the stomach (observed/expected, 1.33; 95% CI, 1.16–1.52) and for primary liver cancer (1.73; 95% CI, 1.29–2.28); statistically significant decreases were found in the mortality rates from cancers of the tongue and mouth (0.52, 0.26–0.93), pharynx (0.35, 0.16–0.66) and colon (0.77, 0.63–0.95) (Table 37). The mortality rate from leukaemia was increased in the period < 10 years since starting work (1.93; 95% CI, 1.19–2.95) but not subsequently. The rate was significantly related to cumulative exposure only for cancer of the pancreas (ERR/WLM, 0.07%; 95% CI, 0.01–0.12) and, in the period < 10 years since the start of employment, for other and unspecified cancers (ERR/WLM, 0.22%; 95% CI, 0.08–0.37). [The Working Group noted that the increases in mortality rates from stomach and liver cancers and leukaemia are unlikely to have been due to radon, since they are unrelated to cumulative exposure. The absence of a biological mechanism for radon-induced pancreatic cancer, coupled with the number of comparisons made in this analysis, points to a chance occurrence. This analysis provides considerable evidence that high concentrations of radon in the air do not materially increase the risk for death from cancers other than lung cancer.]

2.1.2 *Residential exposure*

In contrast to the studies of underground miners, which were usually cohort studies, studies of the effects of residential exposure to radon have usually been case–control studies, because detailed residential and smoking histories must be obtained for each subject. In a number of early studies, residential radon concentrations were assessed by indirect measures, such as housing characteristics (for a review, see Committee on Health Risks of Exposure to Radon (BEIR VI), 1999), but in all the more recent studies, the radon concentration was measured directly in the air of the subjects' homes with α-track detectors and imputation of missing values. These measurements were then used to calculate a time-weighted average (TWA) concentration of radon during an appropriate exposure time.

(*a*) *Lung cancer*

These studies were reviewed in detail by the Committee on Health Risks of Exposure to Radon (BEIR VI; 1999). The summaries given below are based on that review and have been updated and modified appropriately; newly published studies are described in similar format.

Table 37. Numbers of deaths observed (O), ratio of observed to expected deaths (O/E) and 95% confidence interval (CI) since first employment for deaths from cancers at selected sites in a pooled analysis of 10 studies of underground miners exposed to radon

Cancer site (ICD-9 code)	O	O/E[a]	95% CI
Tongue and mouth (141, 143-145)	11[b]	0.52	0.26–0.93
Salivary gland (142)	4	1.41	0.39–3.62
Pharynx (146-149)	9[c]	0.35	0.16–0.66
Oesophagus (150)	45	1.05	0.77–1.41
Stomach (151)	217[c]	1.33	1.16–1.52
Colon (152-153)	95[b]	0.77	0.63–0.95
Rectum (154)	60	0.86	0.66–1.11
Liver, primary (155.0, 155.1)	50[c]	1.73	1.29–2.28
Liver, unspecified (155.2)	3	0.43	0.09–1.26
Gall-bladder (156)	19	1.23	0.74–1.92
Pancreas (157)	91	1.05	0.85–1.29
Nose (160)	3	0.69	0.14–2.02
Larynx (161)	38	1.21	0.86–1.67
Bone (170)	10	1.04	0.50–1.91
Connective tissue (171)	5	0.82	0.27–1.91
Malignant melanoma (172)	18	0.92	0.54–1.45
Other skin (173)	9	1.60	0.73–3.03
Prostate (185)	83	0.88	0.70–1.09
Testis (186)	6	0.72	0.26–1.57
Bladder (188, 189.3-189.9)	39	0.85	0.61–1.16
Kidney (189.0-189.2)	44	0.91	0.66–1.22
Brain and central nervous system (191, 192)	52	0.95	0.71–1.25
Thyroid gland (193)	2	0.47	0.06–1.71
Non-Hodgkin lymphoma (200, 202)	36	0.80	0.56–1.10
Hodgkin disease (201)	17	0.93	0.54–1.48
Multiple myeloma (203)	26	1.30	0.85–1.90
Leukaemia (204–208)	69	1.16	0.90–1.47
Leukaemia excluding chronic lymphoid (204–208 except 204.1)[d]	36	1.11	0.78–1.54
Myeloid leukaemia (205,206)[d]	27	1.41	0.93–2.05
Acute myeloid leukaemia (205.0, 205.2, 206.0, 206.2)[d]	12	1.16	0.60–2.02
Other and unspecified	118	1.12	0.93–1.35
All cancers other than lung (140-161, 163-208)	1179	1.01	0.95–1.07

From Darby *et al*. (1995b)

[a] Expected deaths calculated from national or local mortality rates; study in China therefore excluded

[b] $0.01 < p \leq 0.05$

[c] $p = 0.001$ (two-sided tests)

[d] For each study, only the time period for which the 8th or 9th ICD revisions were in use nationally is included.

(i) *New Jersey, USA*

Schoenberg *et al*. (1990) studied cases selected from 1306 histologically confirmed cases of lung cancer diagnosed in women in August 1982 through September 1983 throughout the State of New Jersey. They were identified from hospital pathology records, the New Jersey State Cancer Registry and death certificate files. In the original study, interviews were held with 532 women and 462 next-of-kin, providing data for 994 women (76% of those eligible). For living cases, controls were selected randomly from files of New Jersey driver's licences (age < 65 years) or Health Care Financing Administration files (age ≥ 65 years). For dead cases, controls were selected randomly from death certificates that did not mention respiratory disease. Controls were individually matched by race, age and, for deceased cases, date of death. Data were obtained at interview for 995 control women (69%). Phase I included subjects who had lived in a single index residence for 10 years or more in the period 10–30 years before diagnosis or selection. Phase II broadened the eligibility period to 5–30 years before interview and targeted all houses in which subjects had lived for four or more years in an area of the State with a high radon concentration and seven or more years in the rest of the State. Subjects were restricted to those for whom nine years or more of residence was known. Under these criteria, 661 cases (66% of the 994) and 667 controls (67% of the 995) were eligible. Measurements representing nine or more years of exposure were obtained for 480 cases and 442 controls, and these were included in the study. Radon was measured with a one-year α-track detector, mainly in the living area. The mean radon concentration was 0.5 pCi/L (18.5 Bq/m^3) for both cases and controls. Exposure was estimated for the 5–30 years before the date of case diagnosis or control selection. The relative risks were increased only in the highest category of exposure (148–418 Bq/m^3; 4.0–11.3 pCi/L), which included five cases and one control (RR, 8.7; 90% CI, 1.3–58). The *p* value for linear trend was significant at $p = 0.05$, on the basis of a one-sided test of the null hypothesis (BEIR VI). The results for cumulative radon exposure were similar to those for TWA concentrations of radon (Schoenberg *et al*., 1992). There was no increased risk with increasing exposure for lifelong non-smokers, but the trend was inconsistent for different smoking groups. [The Working Group noted that a one-sided test of the null hypothesis and 90% confidence intervals were reported. Significance would be approximately doubled and confidence intervals wider if the conventional two-sided tests and 95% confidence intervals had been used. As few subjects had appreciable exposure, the power of the study to detect an effect is low. Further, only 50% of the 1306 women with lung cancer contributed to the study.]

(ii) *Shenyang, China*

A study by Xu *et al.* (1989) and Blot *et al.* (1990) included all female residents of Shenyang, China, aged 30–69 years, in whom primary lung cancer was diagnosed between 1985 and 1987 and who were listed in the Shenyang Cancer Registry. All the diagnoses were reviewed. Controls were selected randomly from the general population in five-year age groups, frequency matched to the cases. A total of 308 cases and 356

controls were interviewed personally, and radon was measured with two one-year α-track detectors in current and previous homes (79% of eligible cases and 91% of controls). The median radon concentrations were 2.8 pCi/L [104 Bq/m^3] for cases and 2.9 pCi/L [107 Bq/m^3] for controls. Exposure to radon was estimated for 5–30 years before case diagnosis or control selection. The relative risk for lung cancer, adjusted for age, education, smoking status and an index of indoor air pollution, showed no significant trend with increasing radon concentration. The patterns of relative risk were the same for different levels of an index of indoor air pollution and after adjustment. When the analyses were restricted to women who had lived for more than 25 years in their last residence, the results were similar to the overall results. The overall dose–response relationship was negative, the lowest risk being seen at the higher exposure (28% were > 150 Bq/m^3).

(iii) *Stockholm, Sweden*

Svensson *et al*. (1989), Pershagen *et al*. (1992) and Lubin *et al*. (1994b) studied 210 cases of lung cancer in women in Stockholm County in 1983–85. Two controls were selected per case: 191 hospital controls and 209 population controls were selected randomly from county population registers and frequency matched on age to the cases. Subjects were interviewed in person or by telephone. Radon was measured for 201 cases and 378 controls with two one-year α-track detectors or a thermoluminescence detector in all homes occupied for two years or more since 1945. The values obtained with the thermoluminescence detector were then adjusted empirically to link them with the α-track measurements (Svensson *et al.*, 1988). The mean concentrations were 3.6 pCi/L [133 Bq/m^3] for the cases and 3.7 pCi/L [137 Bq/m^3] for the controls. Exposure was estimated from 1945 to five years before interview. There was a significant ($p = 0.05$) increase in relative risk with increasing TWA radon concentration in a trend test based on the median radon concentration in each category, but this was reduced to $p = 0.46$ when the continuous value for radon concentration was used. The results based on cumulative exposure were similar to those based on TWAs. There were no clear differences in trend for the various histological types; however, the effect was stronger for non-smokers than for smokers. In contrast to the results for underground miners, the apparent risks were higher when exposure had occurred many years in the past, when exposure assessment was uncertain. [The Working Group noted that the discrepancy between the significance level based on the median radon concentration in each category and that based on individual values is surprising. The explanation may lie partly in the fact that the categorical measure gives lower weight to extremely high values, thus effectively correcting in part for measurement error (see below).]

(iv) *Sweden*

Pershagen *et al*. (1994) and Lagarde *et al*. (1997) studied 1500 men and women aged 35–74 years in whom primary lung cancer was diagnosed between 1980 and

1984, who were selected from the Swedish Cancer Registry. The study included all 650 women and a random sample of 850 men who had been living in Sweden in January 1947 and some time during 1980–84. After various exclusions, 586 women and 744 men remained. Two controls were selected: one control group (730 women and 694 men) was derived from a randomly selected sample of population registers, frequency matched on age and calendar year of residence to the cases; and another control group (650 women and 773 men) was similarly selected but was also matched by vital status against the Swedish Cause of Death Registry. Individuals who had died from smoking-related diseases were not included. A total of 1281 cases and 2576 controls were enrolled. Radon was measured with two three-month α-track detectors in all homes occupied for two or more years since 1947. The mean concentration for cases and controls combined was 2.9 pCi/L [107 Bq/m^3]. The results showed a significant ($p < 0.05$) increase in relative risk with increasing radon concentration, and the excess relative risk was 0.10 per 100 Bq/m^3 (95% CI, 0.01–0.22) (Pershagen *et al.*, 1992). No difference in relative risk trends was observed by cell type or by smoking status.

(v) *Winnipeg, Canada*

Létourneau *et al*. (1994) conducted a study in which the eligible cases were all residents of Winnipeg, Canada, 35–80 years old, in whom histologically confirmed primary lung cancer was diagnosed in 1983–90 and who were listed in the Provincial cancer incidence registry. Controls were randomly selected from the Winnipeg telephone directory and individually matched on age within five years and sex. A total of 738 case–control pairs was included. Proxy interviews were held for 257 cases and 78 controls. Radon was measured with two sequential six-month α-track detectors. The mean concentrations in bedrooms were 3.1 pCi/L [115 Bq/m^3] for cases and 3.4 pCi/L [126 Bq/m^3] for controls. Exposure was estimated for 5–30 years and 5–15 years before the date of case diagnosis or control selection. There was no significant trend in relative risk by concentration of radon in bedrooms or basements. The relative risks were similar and showed no increase by cell type. Smoking patterns were used only for adjustment, and the effect of smoking on the relative risks was not evaluated. [The Working Group considered that the authors did not perform analyses based on a suitably weighted average of radon concentrations in bedrooms and basements. This would have reduced the impact of random measurement error.]

(vi) *Missouri, USA (study I)*

Alavanja *et al*. (1994) carried out a case–control study of 618 women aged 30–84 years who had never smoked or who had ceased smoking at least 15 years previously, and in whom primary lung cancer was listed in the Missouri Cancer Registry in 1986–91. Population-based controls (1587) were selected from State driver's licence files or files of the Health Care Finance Administration, frequency matched by age. After refusals and other exclusions, 538 cases (83%) and 1183 controls (78%) for whom at least one home had been measured for radon in the 5–30 years before

enrolment were included. For case subjects, 63% of interviews were conducted with next-of-kin. Radon was measured with two one-year α-track detectors in all homes in Missouri occupied for one year or more 5–30 years before the date of enrolment. The mean value was the same for cases and controls (1.8 pCi/L [67 Bq/m^3]). In about 7% of the homes, the concentration was > 4 pCi/L [148 Bq/m^3]. There was no significant trend in age-adjusted relative risk with increasing radon concentration. The results of analyses of cumulative exposure were similar. No difference in the trend in relative risk with radon concentration was observed between women who had never smoked and former smokers. The study is somewhat unique in including only incident cases of lung cancer in non-smokers and exposure measurements made close to the date of diagnosis.

(vii) *South Finland*

Ruosteenoja (1991) and Ruosteenoja *et al*. (1996) carried out a case–control study of 238 men with primary lung cancer in 19 municipalities in Finland in 1980–85. For 1980–82, cases were obtained from the Finnish Cancer Registry; for 1983–85, cases were obtained from records of treatment hospitals. A population-based random sample served as controls, frequency matched by age category to the cases. On the basis of information on smoking from a mailed questionnaire, a random sample of 50 lifelong non-smokers, 50 ex-smokers and 395 current smokers was selected to serve as controls. Interviews were carried out with next-of-kin for 85% of cases and 16% of controls. Radon was measured with two-month α-track detectors in all homes that had been occupied for one year or more in 1950–75. Exposure was estimated for the 25 years between 1950 and 1975, that is, 5–10 years before diagnosis of the case or control interview. The relative risks increased with increasing radon concentration, but the trend was not significant ($p > 0.05$). No clear differences by histological cell type were observed, and adjustment for smoking had little effect on the pattern of relative risks with radon concentration.

(viii) *Finland*

Auvinen *et al*. (1996, 1998) studied subjects selected from the Finnish Population Registry of persons who had lived in the same single-family house from 1 January 1967 or earlier until the end of 1985. Between 1 January 1986 and 31 March 1992, 1973 cases of lung cancers were diagnosed. For each case, at least one control was matched by birth year, sex and vital status at the time of diagnosis of the case, yielding 2885 controls. Data were obtained from next-of-kin for 85% of case subjects and 10% of control subjects. For the matched analysis, 517 pairs were available. Radon was measured with one α-track detector, which was mailed to each subject with instructions to place it in the bedroom or in the living room. The mean concentrations were 2.8 pCi/L [103 Bq/m^3] for cases and 2.6 pCi/L [96 Bq/m^3] for controls. Exposure was estimated for 38 median years in the index house for cases and 35 median years in the index house for controls. The initial results, reported by Auvinen *et al*. (1996), were

found to be in error, and corrected results were reported by Auvinen *et al.* (1998). There was no significant trend in relative risk with increasing radon concentration. The relative risk patterns were also similar by cell type and within smoking categories.

(ix) *Israel*

Biberman *et al*. (1993) conducted a hospital-based case–control study with two groups of consecutive patients with primary lung cancer at an oncology ward in the Rambam Medical Center in 1985–89. The groups consisted of 35 cases of small-cell carcinoma among both people who had ever and never smoked and 26 cases of non-small-cell carcinoma (16 adenocarcinomas) in people who had never smoked. The case subjects had to have lived in Israel for at least 10 years before diagnosis. The controls were patients without lung cancer matched by sex and five-year age group who were admitted to the same hospital immediately after admission of the case and had lived in Israel for 10 years or more. After exclusions and refusals, only 35 matched pairs (20 small-cell cancer and 15 non-smokers) were available for analysis. Some information was obtained from the subjects themselves and some from proxies, but details were not given. Radon was measured with α-track detectors placed for an average of nine months between June or July 1990 and April 1991. The overall mean concentration was 1.0 pCi/L [37 Bq/m^3]. No limit was defined for exposure estimation, but only measurements obtained in current housing were used: 28 (80%) cases and 19 (54%) controls had lived for 20 years or more in a house in which measurements had been made, and 15 (43%) cases and 13 (37%) controls had lived for 30 years or more in such a house. No significant differences in median radon concentrations were observed between cases and controls.

(x) *Port Hope, Canada*

Lees *et al*. (1987) studied 27 cases of lung cancer diagnosed in 1969–79 in persons who had lived for seven years or more in Port Hope, Ontario, and who had never been employed at the uranium-refining plant. The controls were 49 subjects matched on sex and date of birth who had lived for seven years or more in Port Hope, at least one of these years during the seven-year period before the date of diagnosis of the matched case. One deceased and one live control were matched to each deceased case, and two live controls were matched to each live case. Neither the mean nor the median radon concentration was provided. Exposure to radon progeny was estimated in all homes occupied in Port Hope since 1933, but residences outside the Port Hope area were ignored. The estimates were expressed in WLM and were adjusted by a background exposure of 0.229 WLM/year. The mean WLM values were 2.7 and 0.5 for cases and controls, including 33% and 49% with 'no' WLM (below estimated background exposure), respectively; the mean WLM values for those exposed were 4.1 and 1.0. With adjustment for smoking, a relative risk of 2.36 (95% CI, 0.79–7.11) for exposed (> 0 WLM) versus unexposed (0 WLM) was found. The authors concluded, however, that radon was not a significant contributor to the lung cancer risk of the general

population studied. [The Working Group noted that details of the radon measurement protocol were not given in the final publication.]

The studies described below are not included in the report of BEIR VI (Committee on Health Risks of Exposure to Radon, 1999).

(xi) *South-west England*

Darby *et al*. (1998) studied 982 white men and women aged < 75 years with lung cancer who had lived in Devon or Cornwall for at least 20 years in the period 5–30 years before diagnosis. Two control groups were selected: one comprised 317 persons who were investigated for suspected lung cancer but were found not to have lung cancer or a disease closely related to smoking, plus 1382 hospital patients admitted to the same hospitals as the patients with lung cancer but for diseases that were not closely related to smoking and matched for age and sex to the patients with lung cancer; and the other comprised 1486 population controls matched by age and sex. All subjects were interviewed in person. The refusal or non-participation rates were 12.4% for patients with suspected lung cancer, 4.2% for hospital controls and 19.0% for population controls. Radon was measured with two α-track detectors placed for six months in all residences in Devon or Cornwall. Annual estimates were derived by the method of Pinel *et al*. (1995). The mean concentrations were 58 Bq/m^3 for cases and 56 Bq/m^3 for controls. Exposure was estimated for 5–30 years before the date of diagnosis (cases) or date of interview (controls). The relative risk tended to increase with increasing radon concentration only in the two highest categories. The estimated excess relative risk per 100 Bq/m^3 was 0.08 (95% CI, –0.03, 0.20). There was no heterogeneity in the trend by cell type or by smoking status. For individuals whose exposure to radon had been covered completely, the excess relative risk at 100 Bq/m^3 was 0.14 (95% CI, 0.01–0.29) before and 0.24 (95% CI, –0.01, 0.56) after adjustment for uncertainties.

(xii) *Missouri, USA (study II)*

Alavanja *et al*. (1999) studied 742 women aged 30–84 years with primary lung cancer who were reported to the Missouri Cancer Registry between 1 January 1993 and 31 January 1994. Age-matched population-based controls were randomly selected from files of driver's licences or lists provided by the Health Care Financing Administration. For analyses with α-track measurements, 247 cases and 299 controls were available. For analyses from surface measurements, 372 cases and 471 controls were used. Two radon measurement protocols were used: one-year α-track detectors and surface monitors. Empirically derived correction factors for the glass-based measurements were used in the homes of smokers or where window glass was used (Mahaffey *et al.,* 1996). The mean concentrations of radon with α-track detectors were 58 Bq/m^3 in kitchens and 56 Bq/m^3 in bedrooms; the mean value with surface measurements was 65 Bq/m^3 in kitchens and bedrooms. Exposure was estimated for 5–25 years before diagnosis (cases) or interview (controls). On the basis of the α-track

measurements, and consistent with the earlier study of non-smoking women in Missouri, there was no significant trend in relation to TWA radon concentration. On the basis of surface measurements, there was a significant trend (p = 0.02), and the relative risk for the category ≥ 148 Bq/m^3 was 3.3 (95% CI, 1.5–7.5) when compared with persons exposed to < 37 Bq/m^3. On the basis of surface monitors, the dose–response relationship for each cell type was similar to the overall result. There was no significant heterogeneity in dose–response by cell type or by smoking status. [The Working Group noted that surface measurement has not yet been validated as a better reflection of cumulative exposure than the α-track technique.]

(xiii) *Iowa, USA*

Field *et al*. (2000) studied 413 women 40–84 years old with primary lung cancer, identified from the Iowa Cancer Registry between 1 May 1993 and 30 October 1996. Population-based controls (614) were selected from State driver's licence files or files of the Health Care Finance Administration and were frequency matched by age. No proxy respondents were available for controls, whereas proxy respondents were necessary and available for 31.5% of the cases. Multiple one-year α-track detector measurements were made in the homes, and radon concentrations outdoors and at the workplace were incorporated into the exposure estimates. Retrospective measurements of radon progeny were performed from window glass. Exposure was estimated for 5–19 years prior to diagnosis for cases or prior to time of interview for controls; the median coverage was 32 years. Overall, a positive categorical trend (p = 0.05) was seen with cumulative radon exposure 5–19 years before death. This was strengthened when the analysis was restricted to 283 live patients and 614 live controls (continuous trend, p = 0.03).

(xiv) *Western Germany*

Wichmann *et al.* (1998a,b) and Kreienbrock *et al*. (2000) studied 1449 incident cases of lung cancer in persons aged < 75 years of age in whom the disease was diagnosed during 1990–95 in southern North-Rhine-Westfalia, Rhineland-Palatinate, Saar or eastern Bavaria and who had never worked in the uranium mining industry. The controls consisted of 2297 people interviewed between 1990 and 1996, who were matched to the cases by age, sex and area and selected randomly from official mandatory registries or by random-digit dialling. In the final analysis, 1023 cases and 1626 controls for whom complete radon measurements were available were included. All of the cases were verified histologically. Radon was measured with two α-track detectors placed for one year, one in the living room and one in the bedroom, in present and past residences (up to 35 years previously). The mean concentrations were 49 Bq/m^3 for cases and 50 Bq/m^3 for controls. Exposure was estimated for 5–15 years before interview. There was no significant trend in risk with increasing TWA radon concentration, and the estimated relative risk at 100 Bq/m^3 was 0.97 (95% CI, 0.82–1.14). The results for cases of small-cell carcinoma were similar to the overall results. For areas with radon concentrations of 67 Bq/m^3 (365 cases) and 60 Bq/m^3

(595 controls), a positive association with lung cancer was seen, but this was not statistically significant. Analyses based on concentrations in current homes were similar to those for concentrations 5–15 years earlier.

(xv) *Eastern Germany*

Wichmann *et al.* (1999) carried out a case–control study in Thuringia and Saxony between 1990 and 1997. Data were available for 2110 cases of lung cancer (73% of those eligible) in five clinics in the area and 1927 population controls (45% of those eligible) matched on sex, age and region. Both patients and controls were < 75 years old. Radon was measured with two α-track detectors. The mean concentrations were 87 Bq/m^3 for cases and 90 Bq/m^3 for controls. Among men, 2.4% of the patients and 26.5% of controls were non-smokers while, among women, 52.8% of the cases and 74.9% of controls had never smoked. The adjusted odds ratio for exposure at 100 Bq/m^3 was 1.04 (95% CI, 0.96–1.12). The test for trend was not significant.

(xvi) *Summary*

Table 38 summarizes the chief features of the major studies of residential exposure to radon and lung cancer that included direct, long-term measurements of radon in the homes concerned. The relative risk for exposure at 100 Bq/m^3, calculated by the Working Group on the basis of published data, and its 95% confidence interval are given for each study. When the results of eight studies were combined in a random-effect model, the summary risk estimate, with heterogeneity taken into account, was [1.09; 95% CI, 1.00–1.19)].

Even in studies in which the radon concentration was measured in the subjects' homes, there is considerable uncertainty in its assessment. In most studies, there are inevitably some residences in which radon cannot be measured, for example because the house has been demolished. In order to calculate an appropriate TWA radon concentration for the subject concerned, therefore, the radon concentration in such residences must be imputed. Radon concentrations also vary seasonally so that, unless average radon concentrations over a full year have been measured, approximate seasonal correction factors must be applied. Even when radon has been measured in a home, the measurements are subject to uncertainty in the sense that repeated measurements on the same residence have a coefficient of variation of around 50% (Bäverstam & Swedjemark, 1991; Lomas & Green, 1994; Lagarde *et al.*, 1997; Darby *et al.*, 1998; Bäverstam & Lagarde, 1999). Statistical theory demonstrates that the effect of such measurement errors is to reduce estimates of harmful or beneficial effects unless special analytical methods that take them into account are used (Cox *et al.*, 1999). Two of the case–control studies of residential exposure to radon and lung cancer were analysed by such methods. In the Swedish study, Lagarde *et al.* (1997) found a relative risk for exposure at 100 Bq/m^3 of 1.17 (95% CI, 1.03–1.37), which is considerably higher than the original estimate of 1.10 (95% CI, 1.01–1.22) (Pershagen *et al.*, 1994) in which uncertainties in the assessment of radon concentrations were

Table 38. Estimates of relative risk (RR) of exposure at 100 Bq/m^3 and 95% confidence intervals (CIs) in epidemiological studies of residential exposure to radon and lung cancer based on at least 100 cases of lung cancer and direct measurements of radon with α-track monitors

Study	Reference	Cases		Controls		RR	95% CI
		M	F	M	F		
New Jersey, USA	Schoenberg *et al*. (1990)	–	480	–	442	1.49[a]	(0.89–1.89)
Shenyang, China	Blot *et al.* (1990)	–	308	–	356	0.95[a]	(undefined–1.08)
Stockholm, Sweden	Pershagen *et al*. (1992)	–	201	–	378	1.16[a]	(0.89–1.92)
Sweden	Pershagen *et al.* (1994)	729	552	1317	1259	1.10[a]	(1.01–1.22)
	Lagarde *et al.* (1997)					1.17[b]	(1.03–1.37)
Winnipeg, Canada	Létourneau *et al.* (1994)	488	250	488	250	0.98[a]	(0.87–1.27)
Missouri, USA (I)	Alavanja *et al.* (1994)	–	538	–	1183	1.08[a]	(0.95–1.24)
South Finland	Ruosteenoja *et al*. (1996)	164	–	331	–	1.80[a]	(0.90–3.50)
Finland	Auvinen *et al*. (1996, 1998)	479	38	479	38	1.11[a]	(0.94–1.31)
South-west England	Darby *et al.* (1998)	667	315	2108	1077	1.08	(0.97–1.20)
						1.12[c]	(0.95–1.33)
Missouri, USA (II)	Alavanja *et al*. (1999)	–	247	–	299	0.85[d]	(0.73–1.00)
		–	372[i]	–	471[g]	1.63[d,e]	(1.07–2.93)
Iowa, USA	Field *et al*. (2000)		413	–	614	1.29[d]	(1.20–1.40)
Western Germany	Wichmann *et al.* (1998a,b)	1214	235	1865	432	0.97[f]	(0.82–1.14)
	Kreienbrock *et al*. (2000)					1.09[g]	(0.86–1.38)
Eastern Germany	Wichmann *et al.* (1999)	926	127	1460	207	1.11[d,f]	(1.00–1.27)
						1.27[d,g]	(1.00–1.60)

All the values except for south-west England and western Germany were calculated by the Working Group from data at 150 Bq/m^3.

[a] Calculated by the Working Group from Lubin & Boice (1997). A meta-analysis based on published data for these eight studies showed a relative risk of 1.09 (95% CI, 1.00–1.19) for exposure at 100 Bq/m^3 (calculated from the values given by Lubin & Boice, 1997).

[b] Assuming 50% coefficient of variation in measured radon concentrations

[c] Assuming 50% coefficient of variation in measured radon concentrations and allowing for uncertainties in estimates of missing values

[d] From Lubin (1999)

[e] Analysis based on surface monitoring

[f] Entire study

[g] Areas with high radon concentrations

ignored. Similarly, in the study in south-west England, an analysis that took into account uncertainties in the radon assessment found a relative risk for exposure at 100 Bq/m^3 of 1.12 (95% CI, 0.95–1.33), which may be compared with an estimate of 1.08 (95% CI, 0.97–1.20) when uncertainties were ignored (Darby *et al.*, 1998).

A further problem is that in some countries residential radon concentrations may have changed systematically over time (Hubbard & Swedjemark, 1993), for example because of the tendency to reduce ventilation rates in indoor air. An alternative to measuring the current radon concentration in the air of all the residences of interest is to use surface monitors to measure the cumulative exposure as recorded in household objects made of glass. This method in principle avoids the uncertainty created by this tendency and also those created by missing values and seasonal corrections. It has been used in one study (Alavanja *et al.*, 1999), in which the relative risk for exposure at 100 Bq/m^3 was estimated to be 1.63 (95% CI, 1.07–2.93). As noted earlier, however, the method has not been validated, and the uncertainties are not inconsequential, especially in homes where subjects smoked.

The estimates of risk from the studies of residential exposure are consistent with predictions based on the risks of underground miners occupationally exposed to radon.

The primary lung tumours found in the male population of the USA consist of squamous-cell carcinoma (32%), adenocarcinoma (27%), small-cell carcinoma and/or oat-cell carcinoma (16%), large-cell carcinoma (8%) and other specified types (5%) (Percy & Sobin, 1983). The histology of the lung cancers in the various case–control studies of residential exposure to radon summarized above parallels this distribution, whereas in uranium miners (especially in the 1950s) small-cell carcinomas represented the majority of cases (Saccomanno *et al.*, 1996; Wiethege *et al.*, 1999).

(*b*) *Cancers other than lung cancer*

Five case–control studies of residential exposure to radon and the incidence of cancers other than lung cancer included at least 40 cases of cancer and long-term measurements of residential radon. The first of these comprised 44 men aged 35–80 who had died from myeloid leukaemia during 1980–89 and who had lived in the province of Viterbo, Italy (Forastiere *et al*., 1998). The cases were obtained from the regional mortality register of Lazio. Five controls per case were selected from among men who had died from other causes during the same period, matched for age. Radon was measured with two six-month α-track detectors in the last home in which the man had lived or in the previous home if he had moved within two years. No significant association between residential radon concentration and the risk for leukaemia was found: relative to < 100 Bq/m^3, the odds ratios for exposure categories 100–145, 146–230 and ≥ 231 Bq/m^3 were 0.51 (95% CI, 0.2–1.3), 0.66 (95% CI, 0.3–1.6) and 0.56 (95% CI, 0.2–1.4), respectively.

The second study included children in whom acute lymphoblastic leukaemia had been diagnosed when they were under 15, who had been treated by physicians

associated with the Children's Cancer Group during 1989–93 and resided in one of nine mid-western or mid-Atlantic states of the USA (Lubin *et al.*, 1998). Controls were selected by random-digit dialling and were individually matched to cases on age, race and the first eight digits of the telephone number. A total of 505 cases and 443 controls were included in the study. For children aged under five years, radon was measured in all homes in which the children had lived for at least six months; for children aged 5–14, radon was measured in homes in which the subjects had lived for at least one year in the five-year period before the reference date. Two α-track detectors were placed for one year in each qualifying residence. The mean radon concentration was lower for case subjects (65.4 Bq/m^3) than for control subjects (79.1 Bq/m^3). For categories of radon exposure of < 37, 37–73, 74–147 and ≥ 148 Bq/m^3, the relative risks based on matched case–control pairs and adjusted for sex were 1.00, 1.22 (95% CI, 0.8–1.9), 0.82 (0.5–1.4) and 1.02 (0.5–2.0), respectively. Other methods of analysis gave similar results.

The third study included children aged < 18 years in whom acute myeloid leukaemia or myelodysplastic syndrome had been diagnosed between January 1989 and March 1993 at member institutions of the North American Children's Cancer Group (Steinbuch *et al*., 1999). In order to be eligible, the index child at the time of diagnosis must have had at least one parent in residence and to have lived in a residence with a telephone and an entrance no higher than the floor above street level. Children with Down syndrome were excluded. One or two controls were selected per case by random-digit dialling and selected on age, race and telephone area code. A total of 173 cases and 254 controls were enrolled. No association was observed between exposure to radon and risk for acute myeloid leukaemia. When compared with < 37 Bq/m^3, the relative risks for categories 37–100 and ≥ 100 Bq/m^3 were 1.2 (95% CI, 0.7–1.8) and 1.1 (0.6–2.0), respectively, after adjustment for maternal race, maternal education, family income and age.

A population-based case–control study on risk factors for childhood malignancies was used to investigate a previously reported association between indoor radon concentration and childhood cancer, with special regard to leukaemia (Kaletsch *et al.*, 1999). The patients were all children under the age of 15 with leukaemia or solid tumours (nephroblastoma, neuroblastoma, rhabdomyosarcoma, central nervous system tumours) diagnosed between July 1988 and June 1993 in Lower Saxony (Germany). Two population-based control groups were matched by age and sex to the leukaemia patients. Radon was measured over one year in homes in which children had lived for at least one year, particular attention being paid to those rooms in which they had spent most of the time. Owing to the sequential study design, measurements could be made in these rooms only for 36% (82 cases of leukaemia, 82 cases of solid tumour and 209 controls) of the 1038 families initially contacted. The overall mean indoor radon concentration (27 Bq/m^3) was lower than those measured in other studies. When a pre-specified cut-off point of 70 Bq/m^3 was used, no association with indoor radon concentration was seen for leukaemia (odds ratio, 1.30; 95% CI,

0.32–5.33); however, the risk estimate was increased for solid tumours (odds ratio, 2.61; 95% CI, 0.96–7.13), mainly on the basis of six cases of central nervous system tumours.

A case–control study of 807 cases of acute leukaemia diagnosed between 1991 and 1996 was carried out in the United Kingdom (Law *et al*., 2000), with 1593 controls matched on sex, age and region. The participation rates were 76% for cases and 65% for controls. Two passive radon detectors were placed in the homes for six months, and 1881 measurements were made. The results of logistic regression modelling showed no association between acute leukaemia and exposure to radon.

2.1.3 *Geographical correlation studies*

(*a*) *Lung cancer*

Many geographical correlation studies have been conducted in an attempt to correlate average radon concentrations with average lung cancer rates in specific areas. These analyses, also called 'ecological studies', have been reviewed comprehensively (Stidley & Samet, 1993; Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). Such descriptive studies are the weakest form of epidemiological investigation because the cumulative exposure of individuals cannot be estimated, nor can important confounding factors such as smoking be controlled for at the individual level. Ecological bias, namely the difference between associations seen at the group level as opposed to the individual level (Piantadosi, 1994; Morgenstern, 1995), has long been recognized as the principal limitation of geographical correlation studies. Further, in the case of radon, population mobility can lead to problems of dose estimation. In some countries, populations move frequently, and the radon concentration in the residence at the time of death does not reflect the TWA of that experienced over the previous 30 years. In addition, as exposure varies widely within small geographical areas, a single summary average for an area is inadequate as an estimate of current, and much less prior, exposure to radon for all the individuals in the area. Nineteen geographical correlation studies on radon have been conducted (BEIR VI), but the best known is the study of Cohen (1995, 2000) in the USA, who reported an inverse correlation between the background levels of radon and mortality from lung cancer in various areas. The age-adjusted mortality rate from lung cancer among white men and white women during the period 1970–79 was compared with the average radon concentrations in living areas of homes in 1601 counties in the USA. Counties were grouped into 18 categories with average radon concentrations of < 12 Bq/m^3 to 220–260 Bq/m^3. The rate of mortality from lung cancer decreased significantly with increasing radon concentration, in contrast to the increasing trend predicted from the data for underground miners.

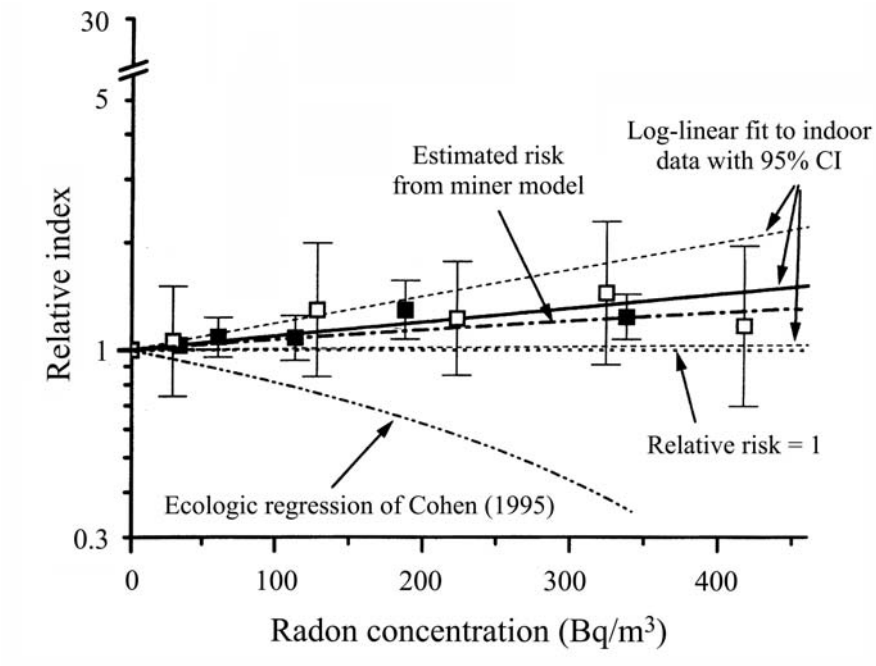
This disparity is striking, and it is not surprising that some researchers have accepted these data at face value, taking them either as evidence of a threshold dose for high-LET radiation, below which no effect is produced, or as evidence that exposure of the lung to relatively high levels of natural background radiation reduces

the risk for lung cancer due to other causes. To those with experience in interpreting epidemiological observations, however, neither conclusion can be accepted (Doll, 1998). Cohen's geographical correlation study has intrinsic methodological difficulties (Stidley & Samet, 1993, 1994) which hamper any interpretation as to causality or lack of causality (Cohen, 1998; Lubin, 1998a,b; Smith *et al*., 1998; BEIR VI). The probable explanation for the correlation is uncontrolled confounding by cigarette smoking and inadequate assessment of the exposure of a mobile population such as that of the USA. It is noteworthy that a positive trend observed in a Swedish case–control study changed to a negative trend when the data were re-evaluated as a geographical correlation study (Lagarde & Pershagen, 1999). Similar differences were noted in Iowa, USA, where Smith *et al*. (1998) reported a negative correlation in the mortality data, which disappeared when incidence data were evaluated, and in southwest England, where substantial ecological bias was observed (Darby *et al.*, 2001). In other words, aberrant dose–response trends in correlation studies disappear when methodologically sounder investigations are conducted within the same geographical regions, based on estimates of individual exposure and control for smoking at the individual level and for other factors that influence lung cancer risk at the geographical level.

It is thus likely that the negative association seen between lung cancer risk and radon concentration in the different areas analysed by Cohen is not due to radon. Uncontrolled confounding by smoking is a probable explanation, as smoking is a predominant cause of lung cancer. Smoking is less prevalent in isolated rural areas of the USA where radon concentrations tend to be higher than in more densely populated areas. Further, confounding is possible because western states include counties with high radon concentrations but low smoking prevalences (Stidley & Samet, 1994). Cohen attempted to allow for differences in smoking by using prevalence data for different states in 1985 and adjusting for changes with time in national data to estimate the prevalence of smoking in the 1970s and then correcting for each county in the states on the assumption that the prevalence varied with the proportion of people living in an urban area and the regression of the lung cancer rate on that proportion. This method of allowing for confounding by smoking is novel but still very crude and inadequate. Even if data on smoking could be obtained for quite small areas, they might still be inadequate for the purpose, as shown by Greenland and Robins (1994), Lubin (1998a,b) and Smith *et al*. (1998). Further evidence for confounding by smoking comes from Gilbert (1994), who noted that other smoking-related cancers were also negatively associated with the radon concentration in Cohen's data.

There is other substantial evidence that contradicts the ecological analyses. The overview of Lubin and Boice (1997), for example, of the results of eight published case–control studies, with individual data on residential exposure to radon and smoking habits, showed a dose–response relationship that was quantitatively similar to that seen for underground miners and statistically incompatible with the negative response reported by Cohen (1995) (Figure 4). That is, when individual exposures to

Figure 4. Summary relative risks from a meta-analysis of case–control studies of residential exposure to radon (open squares) and from a pooled analysis of studies of underground miners (filled squares), restricted to exposures to < 0.175 J h/m^3 (50 WLM)



From Lubin and Boice (1997) and Committee on Health Risks of Exposure to Radon (BEIR VI) (1999)

radon were estimated and smoking was controlled for, there was no evidence of a decreasing lung cancer risk at the concentrations experienced indoors.

It should be stressed that data on radon and the many potential confounders considered in Cohen's correlation studies are averages for geographical areas. Risk estimates from such studies are vulnerable to biases that are not present in estimates based on individual data, such as from cohort or case–control studies. In particular, Greenland and Robins (1994) pointed out that a lack of confounding in group data need not imply the absence of confounding in data for individuals, and vice versa. This is particularly true in the case of indoor radon, since smoking has a much greater impact on lung cancer risk than radon. Furthermore, the data available from correlation studies do not take account of residential history. For example, a person who had just moved into an area from one with a different radon concentration would be categorized solely by the current area of residence rather than by the cumulative or time-weighted average exposure which is obtained in case–control evaluations. Indeed, as mentioned above, residential radon concentrations vary widely, even within geographical areas. While it

is true that the geographical correlation studies have less statistical uncertainty because the numbers are so large, greater statistical precision must be viewed in the context of the greater potential for substantial bias. The estimates of risk may be very precise, but they are nevertheless substantially biased, i.e. incorrect.

The overall evidence and an evaluation of the methodological aspects of the studies indicate that the data on miners provide a sound basis for estimating the risk associated with exposure to radon, at least under occupational conditions (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). The results of the case–control studies of indoor exposure to radon are consistent with the risk estimated from the studies of underground miners (Lubin & Boice, 1997; Figure 4). Geographical correlation studies are of little value in estimating the risks association with exposure to radon because individual exposures are unknown and residential mobility and lack of control of smoking are severe methodological limitations (and probable explanations for the peculiar trend in the low dose range). The weight of evidence is that the ecological analyses of Cohen can be rejected. The interested reader is referred to the lengthy discussions by the BEIR VI Committee in reaching this conclusion (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999).

(*b*) *Cancers other than lung cancer*

BEIR IV (Committee on the Biological Effects of Ionizing Radiations, 1988) and BEIR VI (Committee on Health Risks of Exposure to Radon, 1999) reviewed the ecological studies of exposure to radon and cancers other than of the lung. Both committees concluded that these analyses were too subject to bias to provide much information on the risk of the general population. Further, their results are inconsistent with those of more comprehensive studies of miners, who received substantially higher doses (Darby *et al*., 1995b), and with those of comprehensive case–control studies of indoor exposure to radon and leukaemia in childhood (Lubin *et al.*, 1998) and adulthood (Law *et al*., 2000).

The ecological or geographical correlation units used in these analyses ranged from counties to countries. One of the first reports was that of Lucie (1989), who found a positive correlation between the average radon concentration and the incidence of acute myeloid leukaemia in counties in the United Kingdom. Henshaw *et al*. (1990) then published estimates of the dose of radiation to the red bone marrow and suggested that a significant part of the dose might be from typical indoor concentrations of radon. Positive ecological correlations were shown between the mean exposures of the populations in 15 countries and the incidences of myeloid leukaemia, childhood cancers and other cancers. No positive correlations were found for skin cancer (Eatough & Henshaw, 1992; Harley & Robbins, 1992; Eatough & Henshaw, 1995). The equivalent dose resulting from exposure to radon at 200 Bq/m^3 for one year might be around 100 mSv to the lung and as high as 25 mSv to the skin, in contrast to the dose to red bone marrow of approximately 0.1–1.2 mSv (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999; National Radiological Protection Board, 2000).

There was substantial criticism of the report of Henshaw *et al.* (1990) (Butland *et al*., 1990; Mole, 1990; Peto, 1990; Wolff, 1991). The dosimetric model was questioned (Mole, 1990), and it was noted that even Henshaw's highest estimate of the dose to the red bone marrow from radon would be only 1% of that to the lung (Butland *et al*., 1990; see also Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). Concerns were raised about confounding and biological plausibility, and it was further suggested that the observations might have resulted from confounding by socioeconomic factors.

Muirhead *et al.* (1991) conducted an ecological analysis of childhood leukaemia based on much smaller areas (districts) in the United Kingdom. They reported no significant association with exposure to radon, even though analyses in aggregated areas (counties) showed a significant positive correlation. It was noted that no correlations were found between districts within counties, whereas correlations were found between counties, again indicating the severe difficulties and methodological limitations of ecological analyses, even for small geographical areas.

Further, analytical epidemiological case–control studies have not found a correlation between childhood acute lymphoblastic leukaemia and residential radon concentrations, measured and estimated for individual children who developed leukaemia and for comparable controls (Lubin *et al.*, 1998). In addition, a recent, comprehensive study of adult acute leukaemia based on case–control evaluations also found no evidence that the incidence of leukaemia was related to measured residential radon concentrations (Law *et al*., 2000). In conclusion, the ecological studies have had little success in either directing useful research to identify potential hazards associated with residential radon or providing quantitative evidence for or against an associated risk.

2.1.4 *Estimation of risk*

Epidemiological studies of underground miners have been the primary basis for estimating the risk associated with indoor exposure to radon. The key uncertainties in the data on miners include the heterogeneous risk estimates in the individual studies, which vary by more than a factor of 10, the effects of errors in exposure estimates on these risks, extrapolation to low exposure, the shape of the exposure–response relationship at low exposure, the consequences of exposures other than radon (including known lung carcinogens such as arsenic) in the mines and modification of the effect of radon by smoking. Furthermore, an interesting inverse dose-rate effect (protraction enhancement effect) is demonstrated at very high cumulative exposure levels, but appears to be inconsequential at the lower exposure experienced in the home (see above). Models for risk extrapolation have been used by the Committee on the Biological Effects of Ionizing Radiation (BEIR IV) (1988) and by the Committee on Health Risks of Exposure to Radon (BEIR VI) (1999), which evaluated and combined 11 studies of miners (Lubin *et al*., 1994a, 1995b, 1997). Meta-analyses of the case–control studies have also been conducted in an attempt to quantify the risks

of radon-induced lung cancer (Lubin & Boice, 1997), but so far have been based only on the published studies. Although the results of the analytical case–control studies are consistent with the predicted low risk extrapolated from the studies of miners, the data from the latter studies form the basis for most public health evaluations.

The combined analysis of 12 studies of underground miners is summarized in section 2.1.1. The large numbers of miners studied, the large excess of lung cancers and the long follow-up permitted modelling of the exposure–response relationship. This modelling extends that of the Committee on the Biological Effects of Ionizing Radiations (BEIR IV) (1988) which provided a combined analysis of four data sets: on the Swedish Malmberget iron miners and on the studies of underground uranium miners in the Colorado Plateau and in Ontario and Beaverlodge (Canada). This modelling approach is based on empirical fitting of the data and not on biological end-points, and is used for risk assessment in relation to indoor exposure to radon by the Committee on Health Risks of Exposure to Radon (BEIR VI) (1999).

(*a*) *Risk models*

A linear ERR model has generally been used to analyse the studies of miners:

$$RR = 1 + \beta w$$

where RR is the relative risk, β is a measure of the unit increase in ERR per unit increase in w, and w is the cumulative exposure to radon in WLM (Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). The Committee on the Biological Effects of Ionizing Radiations (BEIR IV) (1988) concluded that a relative-risk model based on time since exposure provided the best fit for the data. The age-specific lung cancer mortality rate, *r (a)*, was expressed as:

$$r(a) = r_o(a)\,[1 + 0.025\,\gamma(a)\,(W_1 + 0.5\,W_2)],$$

where $r_o(a)$ is the age-specific background lung cancer mortality rate; $\gamma(a)$ is 1.2 when age a is < 55 years, 1.0 when a is 55–64 years and 0.4 when a is ≥ 65 years. W_1 is the WLM received 5–15 years before age a; and W_2 is WLM received ≥ 15 years before age a. No radon-related lung cancer risk is assumed for exposures received five years before age a. This is a multiplicative model of the background, or naturally occurring, rate, and it is assumed that other factors that determine lung cancer risk, e.g. tobacco use, are multiplicative with those of exposure to radon. This approach allowed the effect of radon exposure to vary within two exposure windows and differs from the so-called 'constant-in-time' relative risk models commonly used for cancer risk estimation in relation to radiation.

The pooled analysis of the 11 studies of underground miners went even further, taking into account that the ERR/WLM varied significantly with other factors (Lubin *et al*., 1994a, 1995b). The ERR/WLM decreased with attained age, time since exposure and time after cessation of exposure, although it was not affected by age at first exposure. The ERR/WLM was seen to increase as the duration of exposure increased

(or as the exposure rate declined) (Lubin *et al.*, 1997). Two models were then developed. Both incorporated time-since-exposure windows and accounted for the modification of the effect of radon by attained age. One incorporated variations in exposure rate (the TSE (time since exposure)/AGE (attained age)/WL (work level)-categorical model), and the other incorporated variations in the duration of exposure (the TSE/AGE/DUR (duration of exposure)-categorical model). These models and their parameters are shown in Table 39.

Table 39. Parameter estimates from recent analysis of pooled data on miners for two summary models

Exposure–age–duration (DUR) model		Exposure–age–concentration (WL) model	
$\beta \times 100$	0.55	$\beta \times 100$	7.68
Time since exposure (TSE) windows		Time since exposure (TSE) windows	
$\theta_{5–14}$	1.00	$\theta_{5–14}$	1.00
$\theta_{15–24}$	0.72	$\theta_{15–24}$	0.78
θ_{25+}	0.44	θ_{25+}	0.51
Attained age (AGE)		Attained age (AGE)	
$\varphi_{< 55}$	1.00	$\varphi_{< 35}$	1.00
$\varphi_{55–64}$	0.52	$\varphi_{35–64}$	0.57
$\varphi_{65–74}$	0.28	$\varphi_{65–74}$	0.29
φ_{75+}	0.13	φ_{75+}	0.09
Duration of exposure (DUR)		Exposure rate (WL)	
$\gamma_{< 5}$	1.00	$\gamma_{< 0.5}$	1.00
$\gamma_{5–14}$	2.78	$\gamma_{0.5–1.0}$	0.49
γ_{15-24}	4.42	$\gamma_{1.0–3.0}$	0.37
$\gamma_{25–34}$	6.62	$\gamma_{3.0–5.0}$	0.32
γ_{35+}	10.2	$\gamma_{5.0–15.0}$	0.17
		γ_{15+}	0.11

From Lubin *et al*. (1997); Committee on Health Risks of Exposure to Radon (BEIR VI) (1999). The fitted model had the form $RR = 1 + \beta (w_{5–4} + \theta_{15–24}\, w_{15–24} + \theta_{25+}\, w_{25+})\, \varphi_{age}\, \gamma_z$, where β is the exposure–response parameter; cumulative exposure is measured in working level months and partitioned into $w_{5–14}$, $w_{15–24}$, and w_{25+} categories defining exposure received 5–14, 15–24 and ≥ 25 years before current age; $\theta_{5–14}$, $\theta_{15–24}$, θ_{25+} are the *relative* contributions from exposures 5–14, 15–24 and ≥ 25 years before, with $\theta_{5–14} = 1.0$; φ_{age} and γ_z denote parameters for multiple categories of attained age; and z represents either exposure rate in WL or exposure duration (DUR).

TSE, time since exposure; AGE, attained age; DUR, duration of exposure; WL, exposure rate in working level

(*b*) *Recent analysis of data on miners*

While the distinct feature of the data on miners is the linearity in response, it has not been clear whether extrapolation to low doses is appropriate because the range of extrapolation is so great. Analysis of the data on low doses suggests that extrapolation from higher doses may not be misleading (Lubin *et al*., 1997).

Another problem was the retrospective assessment of underground exposure to radon and radon progeny. Mines were rarely ventilated and few measurements were made. In many of the newer studies, substantial numbers of miners were exposed to < 100 WLM, and these studies incorporated extensive information on radon concentrations that reduces the potential for bias due to inadequate exposure assessment.

Departures from linearity have also been observed or suggested at the highest and lowest exposure levels. In the study of miners in the Colorado Plateau and some other studies, the risk for death from lung cancer flattened out at the highest concentrations of radon and radon progeny, probably because of errors in dosimetry, bronchial cell killing by α-particles or wasted dose (i.e. after a tumorigenic dose has been delivered, subsequent exposures have no effect). These very high exposures were excluded from the low-dose analysis. In the lower dose regions, however, a convex dose–response relationship adequately described some of the data, although not significantly better than a linear fit. Any such curvilinearity for the relationship between exposure to α-particles and lung cancer would imply less confidence in the assumption that linear extrapolation would be conservative, as is usually assumed for low-LET radiations. While the current analysis does not rule out curvilinearity, the slight departure from linearity would appear to have a minimal impact on risk. For completeness, it should be mentioned that the risk estimates from data on miners exposed to low doses do not take into account their exposure to indoor radon (Lubin *et al.*, 1997). Such considerations suggest that the risks may be overestimated by 10–20%, but the general conclusions are unchanged (Lubin, 1998c).

There is the perplexing observation that the same total exposure delivered over long periods was more strongly carcinogenic than the same cumulative exposure delivered over a shorter period. It is now clear, both epidemiologically (Tomášek *et al.*, 1994a; Lubin *et al.*, 1995b) and radiobiologically (Brenner, 1994), that this phenomenon does not hold or has little influence at the very lowest exposure that might be experienced by most miners today or at residential exposure levels. The absence of an inverse exposure–rate effect at low exposure is perhaps most noteworthy in the study of miners in western Bohemia, Czech Republic, in which the ERR/WLM, after exposure to < 10 WL, did not depend on duration of exposure (Tomášek *et al.*, 1994a).

The recent analysis of the data on miners by Lubin *et al.* (1997) is thus reassuring, in the sense that the estimates of risk based on data for lower doses are not higher than those based on the full range of data. The ‘lower’ exposure range, of course, is not necessarily low in terms of dose to the lung since 50 and 100 WLM probably result in 2.5 and 5.0 Sv, respectively, on the basis of complex assumptions of the conversion of WLM to Gy and of the relative biological effectiveness (RBE) (National Academy of Sciences, 1991).

(*c*) *Generalizability*

The validity of applying estimates of risk from studies of underground miners to the general population, however, relies not so much on the high dose to low dose assumption as on generalizability. Difficulties in generalization include the application

of data on men to women and children; the effects of heavy smoking and mine contaminants such as arsenic, diesel and blasting fumes and silica; differences in breathing rates and attached particles and assumptions of radioactive decay equilibrium (National Academy of Sciences, 1991; Committee on Health Risks of Exposure to Radon (BEIR VI), 1999). Because such issues are difficult to resolve, great importance is placed on combining existing and on-going studies of indoor exposure to radon and lung cancer in order to validate the estimates of risk for underground miners. The results of recent meta-analyses of over 4000 lung cancer cases in eight studies are still somewhat equivocal, but the patterns of risk over categories of indoor radon concentrations appear to be remarkably consistent with those estimated from the studies of miners, and a significant dose–response relationship is seen (Lubin & Boice, 1997). The results of subsequent studies in the United Kingdom (Darby *et al*., 1998) and Iowa, USA (Field *et al*., 2000), are generally consistent with those of the early meta-analysis. Although important questions linger about the generalizability of the estimates for miners to the general population, international cooperation between investigators in Austria, Belgium, Canada, China, the Czech Republic, Finland, France, Germany, Italy, Sweden, the United Kingdom and the USA has continued to provide extremely valuable information on lung cancer risks associated with exposure to radon and radon decay products.

2.2 Radium

2.2.1 *Occupational exposure: Radium-dial painters*

The availability of paints made fluorescent by the addition of small amounts of radium salts led to their use on instrument, clock and watch dials in the early 1900s (see section 1.2.2(*k*)). In the USA, almost 5000 workers, the vast majority of them women, were employed in the luminizing industry (Fry, 1998). Employment was greatest between 1915 and 1930 and between 1940 and 1954, and essentially ceased after 1974.

Fluorescence was initially achieved by the addition of ^{226}Ra salts to paint; later, a mixture of ^{226}Ra and ^{228}Ra (mesothorium) was used in some factories (Fry, 1998). Radioactive decay of these isotopes of radium leads to emission of α-particles, β-particles and γ-radiation at various stages in the decay chain. The two isotopes differ, in that ^{226}Ra has a radioactive half-life of 1600 years and decays to ^{222}Rn (radon), a noble gas with a half-life of 3.8 days, whereas ^{228}Ra has a half-life of 5.75 years and decays to the noble gas ^{220}Rn (thoron), which has a half-life of 55.6 s (see section 1).

The dial painters employed during the early years of the industry had the greatest risk for internal exposure because of the common practice of ‘pointing’ the brush tip with the lips, which led to ingestion of radium. Ingested radium retained in the body migrates to bone tissue: first to the endosteal layer and from there into the mineral matrix. Ingestion of radium may also result in exposure of soft tissues, including the stomach, pancreas, lung, liver and colon (Stebbings *et al.*, 1984). The daily intake of

radioactive materials of these workers by ingestion was estimated by Martland *et al.* (1925) to be 3–43 μg; however, the radium intake may have varied substantially among individuals since ingestion was related to personal work habits (Stebbings *et al.*, 1984). Pointing was discouraged from about 1926 because of concern about possible health hazards and the suspicion that occupational exposure led to health problems, notably necrosis of the jaw, among radium-dial painters (Keane *et al*., 1986).

Cohort studies of radium-dial painters in the USA were initially carried out at the Massachusetts Institute of Technology (Evans *et al*., 1969) and the Argonne National Laboratory (Stebbings *et al*., 1984). In 1969, the two studies were combined and transferred to the Argonne Center for Human Radiobiology. Rowland *et al*. (1983) reported on the incidence of bone sarcoma among 3055 female radium-dial workers who entered the industry before 1950. Among 1468 women who survived more than five years after the beginning of employment and whose radium body burdens had been measured, 42 bone sarcomas were seen, with 0.4 expected. About 50% of these workers were identified by themselves or by co-workers (Rowland *et al*., 1978a; Stebbings *et al.*, 1984); some measurements of radium body burden, or exhumation, may have been conducted because cancer was diagnosed. Consequently, concern was raised that diseased workers may have been more likely than non-diseased workers to have been monitored (Rowland *et al*., 1978a). In order to minimize such a possibility, a second analysis was conducted only of cases observed two or more years after the first measurement of body burden. Among 1257 eligible women, 13 bone sarcomas were observed, with 0.2 expected. The two analyses clearly indicate an excess of bone sarcoma among women with measured body burdens of radium.

The bone sarcomas were widely distributed throughout the skeleton, unlike those typically seen in unexposed subjects, and this suggested a causal agent such as radium incorporated in the bone tissue. Cancers of the paranasal sinuses and mastoid process (head) occurred mainly among subjects exposed to ^{226}Ra only, and infrequently among those exposed to both ^{226}Ra and ^{228}Ra. High ^{222}Rn levels were found in the mastoid cavity of subjects whose body burdens were primarily from ^{226}Ra, leading to the conjecture that radioactive decay of ^{222}Rn released into the cavity by decay of ^{226}Ra in the surrounding bone, and subsequent decay of the progeny of ^{222}Rn, were responsible for the excess incidence of head carcinomas. The short half-life of ^{220}Rn would preclude much migration of this isotope, and hence its decay products, into the paranasal sinuses and mastoid process (Evans, 1966). Rowland *et al*. (1978b) noted that a subgroup of 58 subjects estimated to have received at least five times more radioactivity from ^{228}Ra than from ^{226}Ra developed 10 bone sarcomas and no head carcinomas, while a second group of 391 subjects estimated to have received at least five times more radioactivity from ^{226}Ra than from ^{228}Ra developed 13 bone sarcomas and 10 head carcinomas.

In addition to comparisons of mortality among radium-dial painters with rates for the population of the USA, internal analyses were conducted in which cancer rates were examined in relation to estimated internal radiation doses. Statistically significant

dose–response relationships were obtained with the dose–response model (Rowland *et al.*, 1978b):

$$I = (C + \alpha D + \beta D^2)\, e^{-\gamma D},$$

where I is incidence of bone sarcoma per person-year, D is the quantity (in μCi) of radium that entered the blood ('systemic intake'), and C the natural incidence of bone sarcoma in the population. The exponential term represents the competing, 'cell-killing' effect of dose-related damage that precludes further cell division and, thus, cancer. A linear ($\beta=0$) variant of the model, in which D represents microcuries of ^{226}Ra, gave a good fit to the head carcinoma data, whereas a pure-quadratic ($\alpha=0$) variant, where D represents microcuries of ^{226}Ra plus 2.5 times microcuries of ^{228}Ra, gave the best fit to the bone sarcoma data. No bone sarcomas were observed at weighted skeletal doses of < 10 Gy (Rowland, 1997). Similarly, no bone sarcomas were observed in the studies of British dial painters who were exposed to lower doses (Baverstock & Papworth, 1985), none of whom engaged in brush pointing.

Rowland *et al*. (1978b) evaluated the relative effectiveness of ^{226}Ra and ^{228}Ra in inducing bone sarcomas (61 cases) and head carcinomas (21 cases) among 1474 female dial painters employed before 1930, in terms of 'systemic intake', defined as the quantity of radium (in μCi) entering the bloodstream. Systemic intake could be estimated for 524 subjects, of whom 38 had bone sarcomas and 17 had head carcinomas. ^{228}Ra was estimated to be 2.5 times as effective as ^{226}Ra, per μCi, in inducing bone sarcoma. This value is in agreement with previous estimates for beagle dogs exposed experimentally (Dougherty & Mays, 1969, see section 3).

Carnes *et al*. (1997) used multiplicative and additive models to study the relationship of exposures to ^{226}Ra and ^{228}Ra and mortality patterns among 820 women occupationally at risk for exposure to radium before 1930 at geographically separated facilities in the USA. The findings with respect to head carcinoma and bone sarcoma confirmed the main conclusions of previous analyses, except that the dose-specific risk for bone sarcoma was higher among women exposed to ^{226}Ra before the age of 20; both ^{226}Ra and ^{228}Ra contributed significantly and independently to the risk for bone sarcoma. This finding is in general agreement with the patterns of risk with exposure at young ages seen in other irradiated populations, including the Japanese atomic bomb survivors.

The suggested carcinogenic mechanism is migration of ^{222}Rn, a decay product of ^{226}Rn but not ^{228}Ra, to the paranasal sinuses and mastoid process and subsequent exposure to α-particles from ^{222}Rn and its decay products. Associations between ingested radium and other cancers are more tenuous. No excess incidence of leukaemia was observed among dial painters in the USA or among dial painters with measured body burdens (Spiers *et al*., 1983); Stebbings (1998), however, noted that leukaemia occurred early in female dial workers, and an excess of leukaemia was observed among male radium-dial workers. Stebbings *et al*. (1984) reported elevated rates of death among female radium-dial workers from several causes of cancer death, including cancers of the colon (SMR, 1.56) and breast (SMR, 1.44) and multiple myeloma (SMR,

2.79), when the mortality rates were compared with those of the population of the USA. Suggestive positive associations were observed between estimated radium body burden and lung cancer, breast cancer and multiple myeloma. The authors noted that lung cancer and multiple myeloma were associated with duration of employment [a surrogate for cumulative external γ-radiation dose (see IARC, 2000)] as well as with radium body burden. The authors postulated that the association with breast cancer was due to confounding, and that an association with exposure to radium was unlikely to be causal because the excess was as high in women who had started work after 1930 (long after 'pointing' had been stopped) as it was in women who had started earlier and had had average radium intakes approximately 100 times higher (Stebbings *et al.*, 1984; Rowland *et al.*, 1989). Further, women who had worked the longest and had had both heavier exposure to γ-radiation from radium and higher breast cancer rates tended to have chosen not to have children. Thus, nulliparity, an important risk factor for breast cancer, might explain a portion of the excess of breast cancer.

2.2.2 *Iatrogenic exposure*

^{224}Radium, historically known as 'thorium X', is a short-lived α-particle-emitting isotope with a physical half-life of 3.62 days, which deposits preferentially in bone. While the largest radiation doses from internally deposited ^{224}Ra tend to occur at the bone surface, its decay products may accumulate in the liver, kidney, spleen, eye and other organs. Soon after isolation of ^{224}Ra in 1902 (Rutherford & Soddy, 1902), there was great interest in its potential therapeutic use. Medical administration of ^{224}Ra has been used for the treatment of chronic arthritis, ankylosing spondylitis, bone tuberculosis and blood diseases (Bickel, 1913).

Between 1944 and 1951, several hundred German children were treated with repeated injections of ^{224}Ra, mostly for the treatment of bone tuberculosis. This treatment proved ineffective against tuberculosis and was discontinued in children in 1951, but it was used later in Germany and in France for the treatment of adult ankylosing spondylitis (Spiess & Mays, 1979a) up to 1978 (Schales, 1978).

Some patients were given relatively high doses of ^{224}Ra mixed with traces of eosin and colloidal platinum (the latter being presumed to 'guide' the radium to the affected tissue). This compound, known as Peteosthor, was used primarily to treat patients with tuberculosis of the bone or ankylosing spondylitis (Troch, 1949; Spiess & Mays, 1979b). The calculated skeletal dose averaged 4.16 Gy (range, 0.06–57.50 Gy), and the average duration of administration was seven months (Mays, 1988). In the early 1950s, objections were raised to treatment of patients with Peteosthor after ^{224}Ra was found to be deposited in the growing zones of the skeleton, thereby causing severe damage to children and juveniles. In addition to growth retardation, malignant bone tumours were observed in patients treated as children (Rathke, 1954; Spiess, 1956).

Other patients were given lower doses of ^{224}Ra, without platinum or eosin, mainly for treatment of ankylosing spondylitis. This treatment was first used on a large scale

at the Orthopaedic University Hospital in Münster, Germany, and was then adopted by other hospitals. The majority of the patients, most of whom were treated in 1948–75, received one series of 10 weekly injections of approximately 1 MBq of ^{224}Ra per injection. This led to a cumulative α-particle dose of 0.56 Gy to the marrow-free skeleton of a 70-kg man (mean bone surface dose, approximately 5 Gy) (Spiess & Mays, 1970, 1971; Wick *et al.*, 1999).

(*a*) *Studies of patients treated with high doses of radium-224*

In 1944–52, about 2000 patients in Germany, mostly children and juveniles, received repeated injections of Peteosthor (Schales, 1978). From 1954, efforts were made to identify and follow-up these patients. The most recent reports (Spiess, 1995; Nekkolla *et al*., 1999, 2000) describe cancers among 899 patients (621 men, 278 women) who received injections of ^{224}Ra, mainly between 1945 and 1955. This study included most of the patients who were treated with high doses of ^{224}Ra (mean bone surface dose, 30 Gy; mean specific activity, 0.66 MBq/kg). Of these, 455 patients (of whom 214 were under 21 years at the time of treatment) were treated for tuberculosis, 392 adults (one under 21) were treated for ankylosing spondylititis, and the remaining 51 patients were treated for other diseases such as polyarthritis and multiple sclerosis.

In recent follow-up studies, a significant excess of cancers at sites other than the skeleton became apparent. The observed cancer rates were compared with those expected on the basis of incidence rates from the Saarland Cancer Registry for the years 1970–94. In the follow-up to 1998, 188 solid malignancies were observed, four of which occurred less than five years after the first injection of ^{224}Ra. Under the assumption of a minimum latency period of five years, an elevated standardized incidence ratio [SIR, 1.23] was observed for solid malignancies (184 cases observed versus 150 cases expected, $p = 0.004$) (Nekolla *et al.*, 1999).

(i) *Bone sarcomas*

In a follow-up study through September 1998, 219 of these patients were still alive (92 women, 127 men). A total of 56 malignant bone tumours had occurred in 55 patients, one person having developed a secondary bone sarcoma two years after the first. Most of the cases occurred within 25 years of exposure, and only four bone sarcomas have been diagnosed since 1980. According to data from the cancer registries of Saarland and of the former German Democratic Republic, the expected number of bone sarcomas in a group of this size would have been less than one (about 0.3) over the entire observation period. The age at first injection of patients with bone sarcomas was between two and 55 years, and the tumour appearance times peaked at eight years after exposure. Younger age at exposure, particularly at ages of active bone growth, appeared to be associated with a higher risk for radiation-induced tumours. Among patients under the age of 21 years, 37 bone sarcomas were reported, whereas among adults 19 bone sarcomas occurred in 18 patients. In the group of ankylosing spondylitis patients, six bone sarcomas were seen (Nekolla *et al*., 2000).

(ii) *Mammary carcinomas*

A significant increase in the incidence of female breast cancer (28 cases observed, eight cases expected) was a notable finding during the recent follow-up. The excess incidence rate in the group of women treated when under the age of 21 years was particularly large (SIR, 9.4 [17 mammary carcinomas observed versus 1.8 cases expected, data extracted from a figure]). In contrast, in the cohort of female patients treated with ^{224}Ra after the age of 21 years, the rate of breast cancer increased by less than twofold (11 compared with 6.2). Seven cases of breast cancer appeared comparatively early, i.e. before the age of 45. The youngest woman to develop breast cancer (age at diagnosis, 28 years) was only two years old when treated with relatively high doses of ^{224}Ra. It should also be noted that two cases of breast cancer occurred in males (compared with 0.2 cases expected). A control group of 182 tuberculosis patients who had not been treated with ^{224}Ra was also established, consisting of patients treated between 1944 and 1954 at the ages of 8–21 years. Seven mammary carcinomas were observed in this group, with 3.8 cases expected, suggesting that factors other than radiation may have contributed to the breast cancer excess seen in the exposed group. The authors pointed out that, while the excess of mammary cancers is striking, there is no indication of dose-dependence, which raises the question of whether the excess is due to factors other than treatment with ^{222}Ra (Papke *et al.*, 1995; Nekolla *et al.*, 1999).

(iii) *Leukaemia*

Leukaemias were observed in eight patients (3.8 expected; $p = 0.04$); however, one case of acute myeloid leukaemia was diagnosed as early as 1.7 years after the first ^{224}Ra injection. Two of the remaining seven cases were chronic lymphocytic leukaemia, which is considered to be unrelated to exposure to radiation; however, this type is included in the expected numbers as well. The occurrence of the seven cases two years or more after the first injection was not statistically significant ($p = 0.08$), and the finding must be considered only suggestive. No dose–response analysis was reported (Nekolla *et al*., 1999).

(iv) *Cancers at other sites*

The incidences of soft-tissue sarcomas, kidney cancer, urinary bladder cancer, liver cancer and thyroid carcinomas appeared to be significantly increased: seven cases of soft-tissue sarcoma, with 0.9 cases expected; 10 cases of kidney cancer, with 4.2 expected; and 14 cases of urinary bladder cancer, with 7.2 expected. In female patients, the excess incidence of kidney cancer was even more pronounced, four cases being observed with 0.8 expected. Liver carcinomas (four hepatocellular, three cholangiocellular) developed in seven patients, with 2.2 cases expected; three cases were associated with pre-existing liver cirrhosis and one with liver fibrosis. Thyroid carcinomas occurred in five patients, with 0.8 expected, all of whom had been children or young adults (aged 11–22) when they were treated with ^{224}Ra (Nekolla *et al.*, 1999).

(*b*) *Studies of patients treated with lower doses of radium-224*

A study of ankylosing spondylitis patients who were treated with lower doses of ^{224}Ra was begun in 1971 (Schales, 1978; Wick & Gössner, 1983; Wick *et al*., 1986; Wick & Gössner, 1993). The lowest dose to the bone surface associated with an osteosarcoma was 9 Gy (Wick *et al.*, 1999). The most recent report (Wick *et al*., 1999) included 1577 ankylosing spondylitis patients from nine German hospitals who received one series of 10 weekly injections of approximately 1 MBq ^{224}Ra each. In contrast to the patients treated with Peteosthor, these patients were exposed only when adult. The cancer incidence was compared with expected numbers based on the 1970–94 data in the tumour registry of Saarland and the 1945–90 data in the Danish Cancer Registry. A control group of 1462 ankylosing spondylitis patients was established with approximately the same age distribution, to provide comparative information on causes of death and on health problems potentially related to the disease itself or to its treatment with drugs. The control group consisted mainly of patients from a hospital known to have refused use of ^{224}Ra treatment. Patients who showed evidence of having been treated with radioactive drugs and/or X-rays during the course of the study were excluded from further evaluation. At the time of reporting, 649 patients in the exposed group and 762 control patients had died. The cause of death was ascertained for 626 exposed patients and for 725 control patients.

(i) *Bone tumours*

Among patients treated with ^{224}Ra, four cases of malignant primary bone tumour (with 1.3 cases expected from general population statistics) were observed: one fibrosarcoma of the bone, one malignant fibrous histiocytoma, one reticulum-cell sarcoma (malignant lymphoma) of the bone and one medullary plasmacytoma (myeloma), originally observed in the bone marrow of the sternum and pelvis. [The Working Group noted that there were no osteosarcomas.] In the control group, only one case, a medullary plasmacytoma, was observed (Wick *et al.*, 1999).

(ii) *Leukaemia*

Thirteen cases of leukaemia were observed among patients treated with ^{224}Ra (with 4.2 cases expected in the general population; $p < 0.001$). In the control group, seven cases of leukaemia were observed, with 5.4 cases expected ($p = 0.3$). Leukaemia occurred among people over 43 years of age throughout the period of observation. Subclassification of the leukaemia cases in irradiated patients showed a predominance of myeloid leukaemia (eight cases observed, with 1.7 cases expected; $p = 0.001$) in the exposed group, which occurred in people aged 46 and older with no peak in the latency. In the control group, three cases of myeloid leukaemia were found, with 2.2 cases expected (Wick *et al.*, 1999). [The Working Group noted that four cases of lymphoid leukaemia were found among people treated with radium, consisting of one acute and three chronic dysplastic leukaemias.] Inferences are restricted by the generally small numbers of cases and the absence of dose–response analyses (UNSCEAR, 2000).

(iii) *Cancers at other sites*

No significant difference between the observed and expected numbers of cases of cancer of the female breast or of the urinary tract, liver or stomach was found.

In conclusion, bone sarcomas were the major late effect in patients who were treated with high doses of ^{224}Ra. In contrast, treatment of ankylosing spondylitis patients with lower doses of ^{224}Ra resulted in a higher risk of leukaemia than of bone sarcoma.

2.3 Thorium

2.3.1 *Occupational exposure*

Thorium ores and purified thorium materials contain ^{232}Th, ^{228}Th and varying amounts of their radioactive decay products. ^{232}Th is an α-particle emitter with a half-life of 1.4×10^{10} years; ^{228}Ra (half-life, 5.75 years), ^{224}Ra (half-life, 3.62 days) and ^{220}Rn (thoron) (half-life, 55.6 s) are among its decay products (Stehney *et al.*, 1980). ^{228}Th is an α-particle emitter with a half-life of 1.9 years (Albert *et al.*, 1955). Fine particles containing thorium and its progeny nuclides may be inhaled by workers in thorium refineries or in mining monazite and rare earth ores. Ore dust containing thorium and its progeny nuclides absorbed through the respiratory organs was deposited mainly directly in the lungs and surrounding lymph nodes, and little was deposited in the liver, kidney or other inner organs (Table 40) (Stehney, 1999). Until the 1950s, no protection against inhalation of ore dust containing thorium and other radioactive nuclides was available for workers (Stehney *et al.*, 1980), and workers in thorium refineries often inhaled up to 30 Bq/m^3 ^{220}Rn, with a maximum of 2×10^{-11} Ci/L [740 Bq/m^3] contained in ore dust (Albert *et al.*, 1955).

A follow-up study on mortality among workers in a thorium processing plant was carried out at the Lindsay Chemical Company in Chicago, USA. The participants were selected from among 4582 employees and were limited to those who had worked in 1940 or later up to 1973. The first survey in 1975 was limited to analyses of 3039 male workers (Polednak *et al.*, 1983), but the second survey in 1982 was extended to 3796 workers (3119 men, 677 women; Liu *et al.*, 1992). The exposure of 84 men to α-particle irradiation from airborne thorium in 1952 was calculated to be [0.1–7.1 Bq/m^3 (mean 0.7 Bq/m^3)] (Stehney *et al.*, 1980). Job classifications and duration of employment were used to provide information on exposure to thorium, and individual doses were not available. In the first survey in 1975, an increased mortality rate from lung cancer was observed, although it was not statistically significant (SMR, 1.44; 95% CI, 0.98–2.02) (Polednak *et al.*, 1983). In the second survey in 1982, which included 3119 male thorium workers, the SMR for lung cancer was significantly increased (SMR, 1.36; 95% CI, 1.02–1.78), but Poisson regression analyses showed no significant effect of selected factors on mortality from lung cancer (Table 41) (Liu *et al.*, 1992). These findings suggest that some etiological factor other than radioactivity from the thorium decay

Table 40. Adjusted concentrations of ^{232}Th (mBq/g) in autopsy samples of former thorium workers[a] and their controls

Subject	Years on job	Lung	Pulmonary lymph nodes	Compact bone	Liver	Kidney
Thorium worker A	6.8	1.74	5.40	0.70	0.17	NR
Thorium worker B	22.9	67.1	1210.0	0.58	0.15	NR
Thorium worker C	23.8	12.1	30.5	NR	0.68	0.066
Thorium worker D	3.1	0.23	3.64	0.15	0.013	0.007
Normal samples[b]	–	0.0125	0.22	0.0039	0.0015	0.0018

From Stehney (1999). NR, not reported

[a] Workers at the thorium refinery of the Lindsay Chemical Company

[b] Geometric mean concentrations in samples from men in two general populations

series and the effects of ore dust are the cause of the significant increase in mortality from lung cancer among male workers. Unfortunately, data on smoking were not available (Stehney *et al*., 1980; Liu *et al*., 1992).

In the Baiyan Obo rare-earth and iron mine in China (see section 1.2.2(*h*)), the total number of miners and staff members in 1994 was 7558 (Chen *et al*., 1986, 2000), of whom about half were exposed to thorium in ore dust. An epidemiological study was begun in 1980 on 2072 miners who had inhaled ore dust containing thorium and its progeny nuclides and about 2000 controls consisting mainly of miners who had inhaled dust-free air. The study was expanded until 1993 to include 2903 miners and 4655 controls and is continuing (Chen *et al*., 1989, 1993, 1999, 2000). The numbers of deaths from lung cancer among 2903 miners who had inhaled thorium in ore dust and 4655 controls were 17 among exposed miners (3.30 expected) and 8 (3.48 expected) among controls. The mortality rate from lung cancer among miners who had inhaled ore dust containing thorium decay series was significantly higher than that of the male population of China (SMR, 5.15; 95% CI, 3.36–7.89); however, the rate in controls was also increased (SMR, 2.30; 95% CI, 1.17–4.51). Therefore, the ratio of the two SMRs, 2.24, was not significantly increased. The significantly higher mortality rate from lung cancer in the two groups than in the Chinese male population was due mainly to the high rate of smoking among the Baiyan Obo miners (80%) (Chen *et al.*, 1999).

2.3.2 *Iatrogenic exposure*

(*a*) *History*

Use of thorium dioxide-containing X-ray contrast media for splenography was introduced into clinical practice in the late 1920s, simultaneously in Japan (Oka, 1930) and in Germany (Radt, 1930). Thorotrast, which was marketed in 1931 (Muth, 1989), is the trade name of a medium consisting of a stabilized 250 g/L (19–20% w/w)

Table 41. Standardized mortality ratios for all malignant tumours and lung cancer among male thorium workers according to selected study parameters

Study parameter	All malignant tumours			Lung cancers		
	No. of deaths	Standardized mortality ratio	95% confidence interval	No. of deaths	Standardized mortality ratio	95% confidence interval
Job classification[a]						
Group 1 (mean, 7.1 Bq/m^3)	113	1.23	1.01–1.47	39	1.38	0.98–1.89
Group 2 (0.9–2.0 Bq/m^3)	19	1.44	0.86–2.24	6	1.37	0.50–2.99
Group 3 (0.1–0.5 Bq/m^3)	21	1.28	0.79–1.96	5	1.12	0.36–2.62
Duration of employment (months)						
≤ 1	55	1.38	1.04–1.80	22	1.80	1.13–2.73
2–12	44	0.99	0.72–1.33	15	1.10	0.62–1.81
≥ 13	29	1.44	1.08–1.88	13	1.16	1.62–1.99
Time since first employment (years)						
< 15	57	1.40	1.06–1.82	17	1.73	1.01–2.77
15–29	67	1.21	0.94–1.54	21	1.17	0.73–1.80
≥ 30	29	1.12	0.75–1.61	12	1.29	0.67–2.25
Year at first employment						
1915–1954	115	1.27	1.05–1.53	33	1.24	0.85–1.74
1955–1973	38	1.21	0.85–1.65	17	1.65	0.96–2.64
Total	153	1.26	1.07–1.47	50	1.35	1.00–1.78

From Liu *et al.* (1992). Involved 2999 selected male workers in the thorium refinery at Lindsay Chemical Company, because the job classification or duration of employment was unknown for 120 workers.

[a] Airborne α-particle activity concentration (see also Stehney *et al.*, 1980)

colloidal solution of ThO_2, 16–19% (w/w) dextrin and 0.15% methyl *para*-hydroxybenzoate as a preservative (Council on Pharmacy and Chemistry, 1932; Andersson, 1997).

Thorotrast was used by instillation or injection for various radiological purposes but was used mainly for roentgenological visualization of vascular structures after intravascular injection. Its most important application was for cerebral arteriography (angiography), for which it was introduced in the early 1930s (Moniz, 1932). It gained widespread usage in most of Europe, Japan and North America until it was replaced by other agents around 1950. It can be estimated from the amounts produced that more than 2.5 million (probably 10 million) people have been exposed (Abbatt, 1979).

(*b*) *Distribution of Thorotrast after intravascular injection*

Intravascularly injected Thorotrast is cleared from the blood in animals within a few hours (see also section 4) (Harrington & Huggins, 1939; Müller, 1968), and in humans most is distributed after < 20 days (Kaul *et al.*, 1986). Only about 1% of injected ^{232}Th and its decay products are excreted in human faeces and urine up to one year after injection. The biological half-life has been estimated to be > 400 years (Hursh *et al.*, 1957).

Injected colloidal Thorotrast is cleared from blood by phagocytosis by macrophages of the reticuloendothelial system, mostly in liver, spleen, bone marrow and lymph nodes. After its initial distribution, Thorotrast tends to aggregate in conglomerates, which amplify with time after injection and with increasing amounts of Thorotrast injected (Kaul & Muth, 1978).

(*c*) *Dosimetry* (see also section 1)

The dosimetry of Thorotrast is relatively well established in comparison with that of other internally deposited radionuclides, mainly because ^{232}Th, once incorporated, is not easily removed from the body. Several measurements are possible, including whole-body counting and measurements of exhaled ^{220}Rn in the breath and ^{232}Th and its progeny in tissues obtained at surgery and autopsy. Many biophysical investigations have been conducted in various countries, the most recent ones in Germany and Japan (Kaul & Noffz, 1978; Ishikawa *et al.*, 1993a,b, 1999). Estimates of the absorbed dose in tissues after Thorotrast injection are based on the amount of ^{232}Th deposited in the target organs, the steady-state activity ratios in the organs of interest, consideration of so-called self-absorption of α-particle energy within conglomerates and the distribution of Thorotrast to organs after injection. These factors and other uncertainties have been taken into account.

Uncertainties about the recorded volume of injected Thorotrast have been noted. In order to improve the dosimetry, parts of the cohorts in the German and Japanese studies were monitored by whole-body counting and/or breath measurement as well as by tissue measurements.

It is well known that a proportion of the Thorotrast injected may be spilled at the injection site, leading to the formation of granulomas with dense fibrosis, called thorotrastomas. In the German study, 245 of 899 patients screened by X-ray for cerebral arteriography developed thorotrastomas at the site of injection, and there are further reports in the literature of 147 cases (van Kaick *et al.*, 1995; Andersson, 1997). However, malignant lesions have been reported only rarely to be thorotrastomas (Liebermann *et al.*, 1995).

The distribution of Thorotrast in the organs, especially the ratio between liver and spleen, does not seem to be a linear function of the injected volume. After injection of larger amounts, a higher fraction is stored in the liver (van Kaick *et al.*, 1984; Ishikawa *et al.*, 1989), but this has not been considered in any of the studies in which risks were estimated.

Through biological processes, Thorotrast particles accumulate and form conglomerates of various sizes within a few years, resulting in non-uniform distribution of the nuclide and radiation dose (Dalheimer & Kaul, 1989). This factor is considered by use of a formula developed by Rundo (1958). Therefore, the distribution and dose of Thorotrast are heterogeneous, although mean organ doses have been adopted in all studies. The mean local dose in the region of potential target cells for tumour deve-lopment has been calculated for various organs with little storage of Thorotrast (Dalheimer *et al.*, 1995) and showed a surprising similarity between mean cellular dose and mean organ dose.

Decay products of ^{232}Th deposited in organs with major deposits can be transferred to other organs. In order to take this phenomenon into account, the steady-state activity ratios of the decay products in relation to the parents must be known for each organ of interest. Extensive work has been done (Rundo, 1956; Hursh *et al.*, 1957; Kaul, 1965; Parr, 1968), and there are no major discrepancies between the ratios from older compilations (Kaul, 1973; Kaul & Noffz, 1978) and more recent ones (McInroy *et al.*, 1992; Ishikawa *et al.*, 1993b). Hence, the ratios compiled by Kaul and Noffz (1978) are now used in dosimetric studies.

Little is known about the intervals in tumorigenesis between establishment of malignant cells and clinical manifestation of the tumour. For long-term irradiation from internally deposited radionuclides, the dose absorbed during the interval between initiation of the malignant process and diagnosis may be irrelevant in terms of carcinogenesis and may be considered ‘wasted’ dose in calculations of the cumulative dose needed for cancer induction (Mays, 1982). Ultrasonographic studies of the growth rate of liver tumours showed great variability (Sheu *et al.*, 1985). The interval corresponding to ‘wasted’ dose for primary liver cancer is assumed to be 10–15 years (Andersson *et al.*, 1994; van Kaick *et al.*, 1995; Mori *et al.*, 1995).

The distribution of injected Thorotrast to different organs is important because it is critical for estimation of α-particle dose and the associated risks in epidemiological studies. Kaul and Noffz (1978) estimated the organ distribution in 7–34 cases in the published literature to be 59% to liver, 29% to spleen, 9% to red bone marrow and 3%

to other organs. However, as pointed out later (Ishikawa *et al*., 1989), although the spleen of patients given Thorotrast undergoes severe fibrosis and its weight is thus significantly reduced, the estimates are based on the organ masses of the standard man, resulting in overestimation of spleen deposition and subsequent underestimation of bone-marrow deposition. A revised organ distribution has been published (Ishikawa *et al*., 1999), with a new averaging method and revised organ masses, on the basis of more cases. Risk estimates were based on those of Kaul and Noffz (1978) adjusted with additional estimates based on the new organ partition.

(*d*) *Epidemiological studies*

The long-term effects of injected Thorotrast have been studied in a number of cohorts. The methodological details of these studies are summarized below and in Table 42, while the results are presented together in the next section. More than 5000 persons injected with Thorotrast during 1929–56 have been followed, but only 198 persons were still alive at the end of the follow-up period.

The largest study was initiated in Germany in 1968, where hospital records from almost 50 hospitals in western Germany revealed approximately 5000 Thorotrast-injected patients in 29 hospitals. Of these, 916 could not be traced, while 1917 had died < 3 years after the injection and were excluded from the study, leaving 2326 patients. Of these, 1427 had died before 1968 and had not been examined. They were followed-up with regard to cause of death in hospital records, doctors' reports, pathology reports and death certificates. The remaining 899 patients have been followed by means of regular clinical examinations and certain para-clinical tests including measurements of external γ-radiation in order to estimate the body content of ^{232}Th (van Kaick *et al*., 1984, 1986a,b, 1989, 1991). Of 5151 controls, 1890 hospital patients who were alive three years after hospitalization, matched by age and sex but not by index disease, were identified and followed; 662 had been examined (van Kaick *et al*., 1991). Approximately 70% of the case patients had received injections of Thorotrast for cerebral angiography, while the remainder underwent angiography of the limbs. The cohort has been followed-up regularly, the latest follow-up being in 1998 (van Kaick *et al*., 1999). The dosimetry is based on whole-body measurements of γ-radiation in a large proportion of the patients and on information about the injected volume of Thorotrast for the rest. Data on the risk for cancer are presented as internal risk ratios.

A study was set up in Denmark in 1949 in which patients who had undergone cerebral angiography with Thorotrast were identified at two neurosurgery departments, resulting in about 1000 patients. A control group of 1480 patients who had undergone cerebral angiography with contrast agents other than Thorotrast was identified, but they were not matched to cases for age, sex or calendar period. Thorotrast-treated patients and controls have been followed up with regard to cause-specific mortality by linkage with the Danish Cause of Death Register and with regard to site-specific cancer incidence by linkage with the Danish Cancer Registry (Andersson *et al*., 1994, 1995a). Furthermore, Thorotrast-treated patients have been followed-up by review of hospital

Table 42. Methodological considerations in five cohort studies of patients treated with Thorotrast

Methodological consideration	Germany (van Kaick *et al.*, 1984, 1986a,b, 1999)		Denmark (Andersson *et al.*, 1994, 1995a)		Japan (Kido *et al.*, 1999; Mori *et al.*, 1999a,b)		Portugal (dos Santos Silva *et al.*, 1999)		Sweden (Martling *et al.*, 1999)	Total	
	Thorotrast-treated	Controls	Thorotrast-treated	Controls	Thorotrast-treated	Controls	Thorotrast-treated	Controls	Thorotrast-treated	Thorotrast-treated	Controls
Period of treatment	1937–47	1937–47	1935–47	1946–63	1931–45	1930–45	1929–55	1930–55	1932–50		
Start of study	1968		1949		1963		1961		1963		
Initial cohort size	5159	5151	1095	1480	412	1649	1931	2258	1117	9714	10538
Eligible for study	2326[a]	1890	999	1480	412	1630	1131	1032	509[b]	5377	6032
Ratio men:women	2.82	2.91	1.23	0.92	Men	Men	1.65	1.43	1.3		
Information available for dosimetry	1163[c]		[990][d]		412[c]		1131[d]		306[d]	4002	
Volume of Thorotrast injected, mL, mean	24		18.7–18.8		10–19		26.3		15.4		
Mean age at injection (years)	29 or 36[e]		37.4		> 20		34.1		35		
Year of end of follow-up	1998		1992		1998		1996		1993		
No. of patients still alive	48	239	40	422	37	481	38	173	35	198	1296

[a] Not including patients who died within the first three years after injection

[b] Not including patients who died within the first year after injection or those who died before 1 January 1952

[c] Dose estimated from information about injected volume of Thorotrast or from biophysical measurements (1 mL of Thorotrast contains 0.2 g (~ 810 Bq) of ^{232}Th)

[d] Dose estimated from information about injected volume of Thorotrast

[e] 29 years, mean age at injection in those who developed liver tumours; 36 years in others

records and other sources relevant for diagnoses of liver cancer (Andersson *et al*., 1994), leukaemia (Andersson *et al*., 1993) and lung cancer (Andersson *et al*., 1995b). For the dosimetry, recorded or estimated volumes of injected Thorotrast were used (individual mean dose to the liver, 3.9 Gy; Andersson *et al*., 1994). The rates of mortality and incidence are given as age-, sex- and calendar period-matched SMRs and SIRs (in comparison with the rates of the general population) and as ratios of the two (SMR:SIR ratios for Thorotrast-treated and control patients).

An epidemiological study was started in Japan in 1963 in which 262 male wounded soldiers were injected intravascularly with Thorotrast and were followed up. An age- and sex-matched control group consisting of 1630 ex-servicemen wounded during the same period was also identified. In addition, 370 patients known from autopsies between 1945–92 to have received Thorotrast have also been analysed (Mori *et al*., 1995). Another series of 150 wounded, Thorotrast-treated ex-servicemen known to have been alive on 1 January 1979 has since been established and followed-up. Men in the control group of the first series who were alive on 1 January 1979 served as the control group (Kido *et al*., 1999). Follow-up was conducted through hospital records. The dosimetry was based on information about the injected volume of Thorotrast and, in some cases, on biophysical examinations. Data on the cause-specific mortality are given as internal age-adjusted rate ratios (Mori *et al*., 1999a,b).

A study was started in Portugal in 1961. Of 2436 persons given Thorotrast, 1052 who received intra-arterial injections (80% for cerebral angiography) were followed-up by means of death certificates and hospital records. Of a control group identified in 1972, consisting of 2086 persons matched for age, sex and index disease who had undergone arteriography with other contrast agents, only 924 had been traced at the time of the last follow-up in 1976 (da Silva Horta *et al*., 1978; Cayolla da Motta *et al*., 1979). The study has recently been reactivated and follow-up extended to the end of 1996. The study now consists of 1931 patients treated with Thorotrast systemically and 2258 unexposed controls. Of these, 1131 (705 men, 426 women) Thorotrast-treated cases and 1032 (607 men, 425 women) controls were successfully traced. The amount of injected Thorotrast was recorded in the hospital records for 90.3% of the patients and varied considerably. The cause of death was obtained at post-mortem examination (25.5% of Thorotrast-treated cases, 10.4% of controls), clinical records and death certificates (dos Santos Silva *et al*., 1999). Data on cause-specific mortality are given as internal age-adjusted rate ratios.

In Sweden, a cohort of 431 patients who had undergone cerebral angiography with Thorotrast was identified, but follow-up has been rudimentary until recently (Blomberg *et al*., 1967). The cohort has now been expanded and followed-up for an additional 30 years (Martling *et al*., 1999). The total cohort consists of 1117 Swedish patients with neurological disorders who received Thorotrast for cerebral angiography during the period 1932–50. A total of 608 patients were excluded from further analyses mainly because of death within one year of examination, leaving 509 patients in the study. Survival through 1 January 1952 was required to allow computerized linkage of the

cohort to the Swedish Cause of Death Register, which was established in that year and contains information on all deaths in the country. Data on cause-specific mortality are presented as SMRs calculated as the ratio of the number of cases observed in the cohort to that expected in the general population. No control group was described. Cancer incidence was analysed by linkage to the Swedish Cancer Registry, but the results of this analysis are not yet available.

In the USA, Janower *et al*. (1972) identified 724 persons who had received Thorotrast for cerebral angiography and a control group of 315 persons who had been exposed to other contrast agents. The cohorts were followed-up only recently, when the study was reactivated, and the results have not yet been published. Smaller groups of Thorotrast-injected patients have been identified and followed for shorter periods in the United Kingdom (Boyd *et al*., 1968) and Canada (Berrett & McRae, 1958).

Numerous case reports of long-term sequels after administration of Thorotrast have also been published.

[The Working Group noted that differences may be seen between the studies since the underlying disease for which Thorotrast was injected varied. In Japan, only wounded soldiers received Thorotrast, whereas in Denmark only neurological patients were treated, and in Germany patients with a variety of diseases were examined. Furthermore, the criteria for matching of controls varied between the studies.]

(*e*) *Mortality from and incidence of cancer*

In general, the cancer risk of Thorotrast-treated cohorts for cancer or death from cancer was increased by three- to fourfold.

(i) *Liver tumours*

The most consistent finding was that the incidence of and mortality from liver cancer in all the studies was highly significantly increased by up to more than 100-fold (Table 43; Andersson, 1997; van Kaick *et al.*, 1999). Almost 800 cases of Thorotrast-related primary liver cancer have been reported in the cohort studies, and approximately 400 cases, not included in the cohort studies, have been reported (Andersson *et al*., 1994). The difference in the relative risk in the Japanese study (36 for mortality) and in the three European studies (71–129; two of mortality and one of incidence) may reflect the fact that the mortality rate from liver cancer is much higher in Japan (annual age-standardized rate per 10^5 among men in 1990, 21) than in Europe (Germany, 4.4; Portugal, 4.1; Denmark, 2.2), and the values for incidence are: Japan, 27.6; Germany, 3.4; Portugal, 4.0; Denmark, 3.9 (IARC, 1998). Liver cancers are usually diagnosed 15 years after Thorotrast administration, and they continue to be the leading cause of death among such patients. In the Danish (incidence), German and Japanese studies, the histological distribution of liver cancer was approximately two-thirds carcinoma (predominantly cholangiocarcinoma) and one-third haemangiosarcoma, which is usually an extremely rare tumour (van Kaick *et al.*, 1986a; Andersson *et al.*, 1994; Mori *et al.*, 1999b). [The Working Group noted the remarkable finding that a similar

Table 43. Numbers and relative risks with 95% confidence intervals (for definitions of relative risk, see footnotes) for cancer at selected sites plus cirrhosis of the liver and all causes of death in five cohort studies of Thorotrast-treated patients

Cancer site	Germany (van Kaick *et al.*, 1999)		Denmark (Andersson *et al.*, 1993, 1995a,b)		Japan (Mori *et al.*, 1999b)		Portugal (dos Santos Silva *et al.*, 1999)		Sweden (Martling *et al.*, 1999)	
	No.	RR[a] (risk)	No.	RR[b]	No.	RR[a] (rate)	No.	RR[a] (rate)	No.	SMR[c]
Liver cancer	454	129[*d]	84	SIR = 121[*] (97–150)	143	36[*] (24–53)	104	71[*] (20–251)		
Cirrhosis of the liver	372	6.0[*]	32	SMR = 7.5[*] (5.1–11)	26	6.9[*] (4.0–12)	50	5.7[*] (3.1–10)	18	13[*] (7.6–20)
Cancer of the bile ducts	29	7.8[*]					3[e]	1.4 (0.4–5.6)		
Gall-bladder cancer	13	2.7	15	Ratio = 17[*] (4.9–110)						
Mesothelioma	9	[f]	7[g]	Risk = 2.5%						
Pancreas	18	2.4[*]	5	2.2 (0.6–7.9)						
Acute myeloid leukaemia	40	4.6[*]	16[g]							
Acute lymphoid leukaemia	2	[f]	1[g]							
Non-chronic lymphoid leukaemia			20	20.35[*] (5.9–127)	10[h]	13[*] (4.5–35)	11	15[*] (1.3–182)		
Myelodysplastic syndrome	30	6.1[*]	7[g]							
Non-Hodgkin lymphoma	15	2.5	2	1.5 (0.2–8.9)						
Hodgkin disease	2	0.8	1	1.6 (0.1–40)						
Myeloma	10 (plasma-cytoma)	4.1	4	4.3 (0.9–31)						
Bone sarcoma	4	3.3	0	–			16	7.1[*] (1.7–30)		
Cancer of the larynx	7	1.9	1	SIR = 1.1 (0.0–6.2)						
Lung cancer	53	0.7	21	1.6 (0.9–2.9)	11	2.0[*] (1.0–3.9)	10	4.7 (0.2–92)		
Cancer of the kidney	10	0.8	5	2.6 (0.7–10.6)						

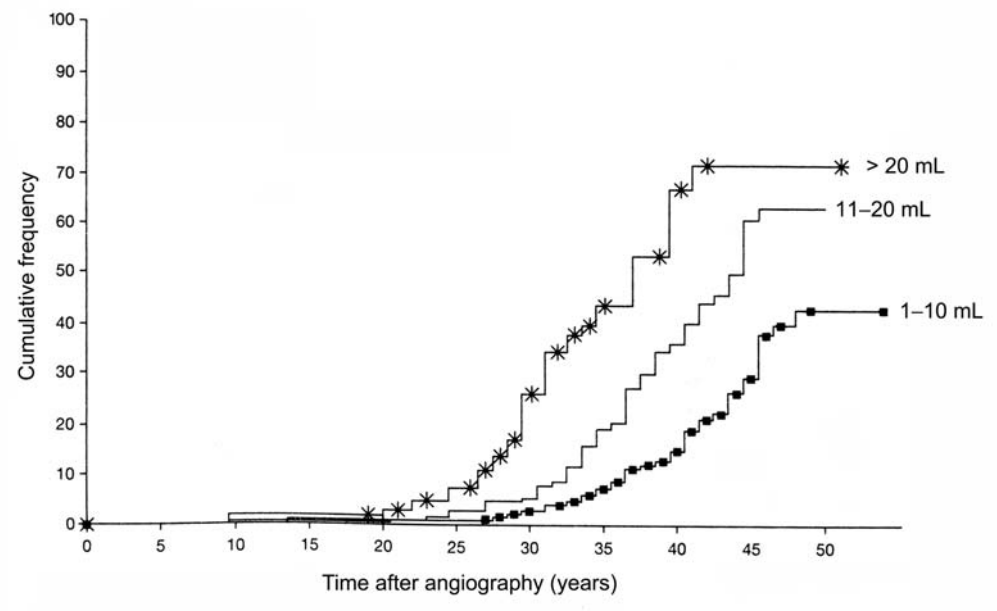
Table 43 (contd)

Cancer site	Germany (van Kaick *et al.*, 1999)		Denmark (Andersson *et al.*, 1993, 1995a,b)		Japan (Mori *et al.*, 1999b)		Portugal (dos Santos Silva *et al.*, 1999)		Sweden (Martling *et al.*, 1999)	
	No.	RR[a] (risk)	No.	RR[b]	No.	RR[a] (rate)	No.	RR[a] (rate)	No.	SMR[c]
Cancer of the urinary bladder	10	1.2	5	0.75 (0.2–2.0)						
Prostate cancer	21	0.9	6	2.98 (0.9–12)						
Central nervous system cancer	19	1.1	21	3.2* (1.6–6.6)			290	1.8 (0.8–4.1)		
All sites of cancer			315	3.2* (2.7–3.9)			509	6.0* (4.4–8.3)	164	4.2* (3.6–4.9)
All causes of death			751	SMR = 3.5* (3.2–3.7)	375	2.5* (2.2–2.8)	988	2.4* (2.0–2.7)	474	2.8* (2.5–3.0)

* $p < 0.05$
[a] Mortality rate (risk) ratio
[b] Ratio of standardized incidence ratios of SIRs (SIR of Thorotrast-treated/SIR of controls, unless otherwise stated)
[c] Standardized mortality ratio
[d] 12.9 in the paper
[e] Bile duct plus gall-bladder
[f] No. in controls, 0; therefore, no RR
[g] Non-register-based data (Andersson *et al.*, 1993)
[h] All leukaemia

histological distribution, with a large number of hepatic haemangiosarcomas, was observed among Russian nuclear workers who inhaled plutonium (see section 2.4.3).] All three studies show a clear relationship between the injected volume of Thorotrast (taken to be equivalent to the dose-rate) and the risk for liver cancer (Figure 5), and it can be assumed that the documented volumes of injected Thorotrast in the hospital records are reasonably appropriate for dose estimation, at least for liver tumours. The cumulative risk estimates calculated from the number of excess liver tumours at the end of these studies agree well. If a 10-year 'wasted' dose is assumed, i.e. patients who died within the first 10 years after Thorotrast injection were excluded since they had no chance to develop liver malignancies, the cumulative risk estimates are 510 per 10^4 person-Gy (Andersson, 1997) in the Danish study, 607 per 10^4 person-Gy (405 with the new dosimetry) (van Kaick *et al.*, 1999) in the German study and 523 per 10^4 person-Gy (Mori *et al.*, 1999a) in the Japanese study. [With a radiation weighting factor of 20 for α-particles, the expected risk for low-LET radiation would be 25.5–30.3 cases per 10^4 person–Sv]. Thompson *et al.* (1994) estimated that the average risk for liver cancer incidence among survivors of the atomic bombings, who were exposed mainly to external radiation, was 1.64 (95% CI, 0.54–2.91) per 10^4 person–years per Sv. [If an exposure period of 30–40 years is assumed, the estimate would be 49–66 cases per 10^4 person–Sv.] These values are similar to those in the

Figure 5. Cumulative frequency of liver tumours with time after angiography in relation to the volume of Thorotrast injected (Kaplan-Meier estimates, log rank test: $p < 0.0001$)



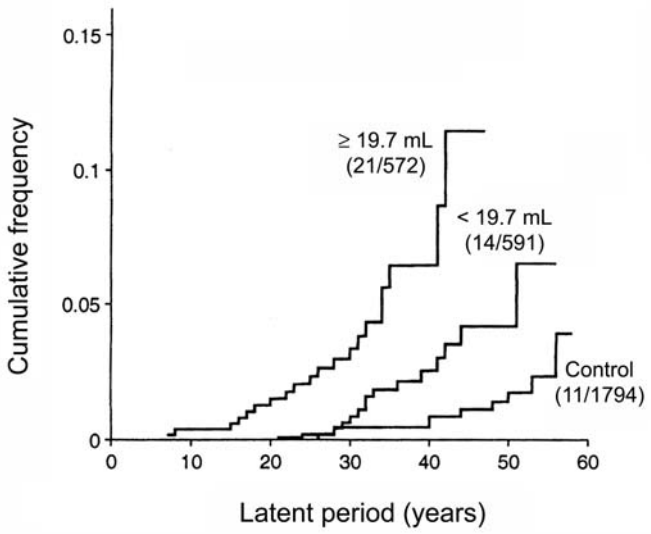
From Andersson (1997)

Thorotrast-treated patients. With a radiation weighting factor of 20, the cumulative risk estimate for liver cancer in the German study was calculated to be 40 per 10^4 person-Sv (van Kaick *et al.*, 1999).

(ii) *Haematological malignancies*

Similarly, the incidence of and mortality from non-chronic lymphoid leukaemia and myelodysplastic syndrome is increased 5–20-fold in Thorotrast-treated individuals, whereas the risk for chronic lymphoid leukaemia was not increased in any study. More than 80 cases of Thorotrast-related non-chronic lymphoid leukaemia were reported in the cohort studies, and more than 40 other cases have been reported (Andersson *et al.*, 1993). An association between the risk for leukaemia and the amount of Thorotrast injected was described in the German study (van Kaick *et al.*, 1999; Figure 6) but not in the Danish study (Andersson *et al.*, 1993, 1995a). Leukaemia was diagnosed approximately five years after exposure. In many studies, most of the cases of acute myeloid leukaemia consisted of erythroleukaemia. The cumulative risk estimates for non-chronic lymphoid leukaemia were 140 cases per 10^4 person-Gy in the Danish study, 135 cases per 10^4 person-Gy in the German study and 129 cases per 10^4 person-Gy in the Japanese study, assuming a 5-year 'wasted' dose. [With a radiation weighting factor of 20 for α-particles, the expected risk for low-LET radiation would be 6.4–7

Figure 6. Cumulative frequency of haematopoietic malignancies (myeloid leukaemia and myelodysplastic syndrome) among persons injected with Thorotrast



The numbers in parentheses are the number of malignancies per number of patients. Note that the frequency and the latency are related to the injection volume (i.e. dose rate) (van Kaick *et al.*, 1999).

cases per 10^4 person–Sv.] Preston *et al.* (1994) estimated that the excess absolute risk for leukaemia among atomic bomb survivors was 2.7 cases per 10^4 person–years per Sv. [If an exposure period of 20–30 years is assumed, the estimate would be 54–81 cases per 10^4 person–Sv.] In contrast to the situation for liver cancer, there is no agreement if a radiation weighting factor of 20 is assumed. [If the fractional deposition of Thorotrast in the bone marrow is assumed to be 25%, as proposed by Ishikawa *et al.* (1999), instead of 9% (Kaul & Noffz, 1978), the risk would be lowered by about 2.5.]

[The Working Group noted that the estimates of the risk for liver cancer associated with exposure to Thorotrast are generally as expected from experimental studies of the RBE of high-LET neutrons (IARC, 2000). High-LET radiations are generally more effective in inducing cancer than low-LET radiations, by a factor of 5–40, and a radiation weighting factor of 20 is used to compute equivalent dose for radiation protection purposes. The estimated risk for leukaemia, however, rather suggests a RBE of 1–2. It should be noted that the difference between low-LET and high-LET in the induction of leukaemia in experimental animals is not as great, and RBEs closer to 1 than to 20 have been reported (Upton *et al.*, 1970; IARC, 2000). It is recognized, however, that RBE is a complex function related to dose, end-point and the radiation qualities and energies being compared.]

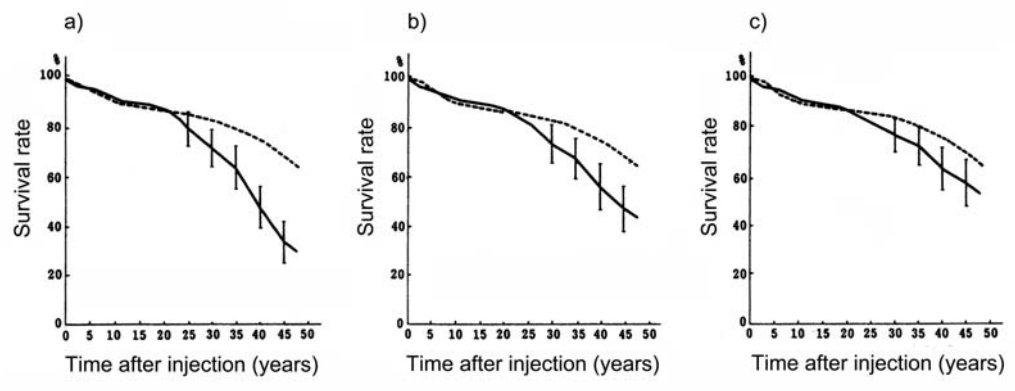
(iii) *Cancers at other sites*

The risks for cancers at other sites were not consistently significantly increased. In some studies, however, significantly increased risks for cancers of the extrahepatic bile ducts, gall-bladder and pancreas and malignant mesothelioma have been reported (Andersson *et al.*, 1995b; van Kaick *et al.*, 1999; see Table 43). Elevated risks for tumours of the central nervous system observed in some studies are presumed to result from selection bias (pre-existing lesions). Although some studies have reported excess frequencies of lung cancer, there is no consistent evidence of an increase in Thorotrast-treated patients, despite the fact that they exhale extremely high concentrations of ^{220}Rn (Grillmaier & Muth, 1971; Kato & Ishikawa, 1992). Interpretation of these data is hampered by lack of information on smoking. The spleen, abdominal lymph nodes and areas with perivascular deposits receive substantial doses, but no increase in cancer risk has been observed.

A significantly elevated increase (6–13-fold) in the rate of mortality from non-malignant liver disorders (cirrhosis) was reported in all these studies (see Table 43).

The German and Japanese studies showed a statistically significant decrease in survival, even after exclusion of the major Thorotrast-related causes of death, liver cancer, liver cirrhosis and haematopoietic malignancies including myelodysplastic syndrome (van Kaick *et al.*, 1989; Mori *et al.*, 1989, 1999b; Figure 7). The implications of this phenomenon have not been interpreted fully yet, but might be explained by slight, but not significant, increases in cancer mortality in various organs and tissues such as the pancreas and pleural and peritoneal membranes.

Figure 7. Survival curves for persons injected with Thorotrast and controls



From Mori *et al.* (1989)
a) All causes; b) excluding mortality from malignant hepatic tumours; c) excluding mortality from malignant hepatic tumours, liver cirrhosis, blood diseases, sarcoma at the injection site, necrotic thorotrastomas, bone sarcoma, lung cancer and epilepsy. Note that the survival rate is still significantly decreased after exclusion of these diseases.

2.4 Plutonium

Studies of workers exposed to plutonium have been conducted in the the United Kingdom and the USA, and studies in the Russian Federation have recently become available. In this section, the word 'plutonium' and the symbol ^{239}Pu refer specifically to the combination of the α-particle emitters ^{239}Pu and ^{240}Pu. ^{239}Pu is the major component of the dose in most circumstances. Smaller contributions to the dose from ^{238}Pu (α-particle emitter) and ^{241}Pu (β-particle emitter, including its decay product, ^{241}Am (α-particle emitter)) are frequently ignored. No epidemiological studies have been conducted on ^{238}Pu or ^{241}Pu. ^{239}Pu has a very long half-life, over 24 000 years, and decays by emitting an α-particle. As α-particles are densely ionizing radiations that penetrate only a few cells before coming to a halt, cells adjacent to the site of deposition of the plutonium receive most of the imparted dose. The distribution of plutonium in the body is such that it concentrates mainly in the liver and skeleton and also in the lung, if inhaled. Experimental studies and knowledge of dose distribution indicate that internally incorporated plutonium would increase the risks for cancers of the lung, bone and liver.

2.4.1 *United Kingdom*

A major study was performed on all 14 319 workers (11 635 men) employed at the Sellafield fuel reprocessing plant of British Nuclear Fuels between 1947 and 1975 (Omar *et al*., 1999), which is on the Cumbrian coast of the United Kingdom and which was originally designed for the production of plutonium for nuclear weapons. Later, plutonium was produced during commercial reprocessing of spent nuclear fuel and has

been stored on the site. The mortality of these workers was studied up to the end of 1992, and cancer incidence was examined from 1971 through 1986. The study included 5203 workers who were monitored for exposure to plutonium, of whom 4609 were assessed for dose. The body burden of most workers was estimated to be < 50 Bq, and only a few had > 1 kBq. The age-, sex- and cause-specific deaths rates for the population of England and Wales were used for comparison. For incidence analyses, cancer registration rates were obtained for both England and Wales and for Cumbria. In addition, rate ratios were calculated for plutonium workers in comparison with other radiation workers, and for all radiation workers in comparison with non-radiation workers. The results of the cancer mortality study are summarized in Table 44. The data in the Table are only for specific cancer sites for which a statistically significant excess (pleura, breast) or deficit (liver and gall-bladder) of deaths was found and deaths from leukaemia and lung and bone cancer. Liver, lung and bone are principal deposition sites for about 90% of plutonium in the body. Leukaemia is included because of its status as a marker disease for exposure to external radiation. [In this cohort, the average cumulative doses from plutonium were 712 mSv to bone surfaces, 194 mSv to lung, 91 mSv to liver and 58 mSv to red bone marrow; a radiation weighting factor of 20 was applied to the absorbed doses to compute equivalent doses in mSv.] The doses to other organs were relatively low. The doses for each worker were calculated by the company by dosimetric models based on the distribution of plutonium activity between organs and its clearance, as recommended by the ICRP (1986) (Riddell *et al.*, 2000). Plutonium workers were defined as those who had ever provided a urine sample for a plutonium assay. As many of these workers were never exposed to plutonium, the dose distribution and average dose are skewed towards low doses.

Assessments of plutonium uptake in the Sellafield study were divided by three to compensate for differences previously observed between the results of urine bioassays and autopsy studies. In Table 44, the number of deaths from all cancers in plutonium workers is not excessive when compared with the death rates in England and Wales (SMR, 1.00). The overall death rates from cancer were also similar when plutonium workers were compared with other radiation workers (rate ratio, 1.05) and when radiation workers were compared with non-radiation workers (rate ratio, 1.06). The numbers of deaths from cancers of the liver, lung and bone were not in excess, but there were significant excesses of deaths among plutonium workers when compared with the rates in England and Wales from cancer of the pleura (SMR, 4.71; $p < 0.001$), breast cancer (SMR, 2.36; $p < 0.05$) and cancers of ill-defined and secondary sites (SMR, 1.44; $p < 0.05$). All the significance tests in this study were one-sided in the direction of the observed difference or trend (Omar *et al.*, 1999).

Eight deaths from malignant pleural mesothelioma occurred in plutonium workers and six deaths in other radiation workers. The increased risk among plutonium workers (SMR, 4.71; $p < 0.001$) and other radiation workers was of similar magnitude (SMR, 3.90; $p < 0.05$) (rate ratio for plutonium and for other radiation workers, 1.15).

Table 44. Observed and expected numbers of deaths from cancers at specific sites among plutonium workers at Sellafield, United Kingdom, rate ratios relative to other radiation workers, and a comparison of all radiation workers with non-radiation workers

Cancer site	Plutonium workers			Rate ratio	
	Observed	Expected	SMR	Pu versus other radiation	Radiation versus non-radiation
Liver and gall-bladder	1	5.17	0.19**	0.85	0.34
Lung	133	145.78	0.91	1.12	0.98
Pleura	8	1.70	4.71***	1.15	∞*
Bone	0	1.10	0.0	–	1.12
Breast	6	2.55	2.36*	7.66**	1.35
Prostate	22	21.36	1.03	0.95	2.21*
Ill-defined and secondary (195–199)[a]	29	20.13	1.44*	1.90*	0.96
Leukaemia	7	9.86	0.71	0.79	1.27
All neoplasms	384	385.10	1.00	1.05	1.06
Person–years at risk		134 817.2			

From Omar *et al.* (1999). Only sites at which significant risks were found and organs with large plutonium deposits are included. SMR, standardized mortality ratio

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

[a] ICD, 8th rev.

Non-radiation workers had no cancers of the pleura (Omar *et al.*, 1999). In an earlier study of workers exposed to external radiation at Sellafield, an increased death rate from cancer of the pleura ($n = 9$; SMR, 4.25; $p < 0.001$) was found. Four more cancers of the pleura were reported among radiation workers (Douglas *et al*., 1994). All nine cancers of the pleura were malignant mesotheliomas (Carpenter *et al*., 1998). Exposure to asbestos is known to be a strong risk factor for pleural mesothelioma, and mesothelioma is pathognomonic for asbestos exposure until proven otherwise. The extent of exposure to this material of employees either at the plant or in other work settings is unknown.

The plutonium workers had higher death rates from breast cancer than other radiation workers (rate ratio, 7.66; $p < 0.001$), but the rate in other radiation workers was significantly lower than that of the population of England and Wales (SMR, 0.34; $p < 0.05$). There were six deaths in plutonium workers and two in other radiation workers (Omar *et al.*, 1999), all among women. A urine sample was taken from one woman for plutonium analysis because of her diagnosis, and she was included among

the plutonium workers' deaths. When this case is excluded from the analysis, the mortality rate from breast cancer among plutonium workers was not significantly greater than that in England and Wales, and the excess in comparison with other radiation workers was of reduced significance ($p < 0.05$).

The mortality rate for ill-defined and secondary cancers in plutonium workers was significantly higher than that in other radiation workers (rate ratio, 1.9; $p = 0.04$), but there was no significantly increased incidence rate nor a relationship between risk and estimated cumulative radiation dose. Trend analyses for plutonium workers related the risk for death from organ-specific cancers to the estimated organ-specific radiation doses from exposures to plutonium and external radiation combined. The only statistically significant finding ($p < 0.05$) was a negative trend between the risk for death from all malignant neoplasms and cumulative radiation dose, assuming no lag period. Analysis of the cancer incidence data revealed no significant increases for plutonium workers when compared with registrations for all neoplasms or all organ-specific cancers in England and Wales. The incidence rate of all neoplasms was the same for plutonium workers and other radiation workers (rate ratio, 0.99). Trend analysis was performed on cancer incidence among plutonium workers in relation to organ-specific plutonium dose plus cumulative external radiation dose. The only statistically significant findings ($p < 0.05$) were positive trends with cumulative dose for all lag periods considered (0, 10 and 20 years), for all lymphatic and haematopoietic neoplasms combined. However, grouping these malignancies with such different characteristics and causes has little biological meaning. The authors concluded that their findings provide no evidence that plutonium increases the risk for cancer in this worker population, who are exposed to relatively low levels (Omar *et al.*, 1999).

Deaths from cancer among 40 761 employees of three United Kingdom nuclear industry facilities, the Atomic Energy Authority, the Atomic Weapons Establishment and the Sellafield plant of British Nuclear Fuels, who had been monitored for exposure to external radiation were examined according to whether the employees had also been monitored for possible internal exposure to tritium (^{3}H), plutonium or other radionuclides (Carpenter *et al*., 1998). For the first two facilities, information was available for the actual years each worker was monitored, while the data from Sellafield were limited to the first year the worker was monitored for ^{3}H and plutonium. Information on individual doses was not available. Among the 12 498 workers monitored for plutonium, 581 died from a malignant neoplasm, giving a significantly lower mortality rate than national rates (SMR, 0.89; two-sided *p* value, 0.005). The SMR for cancers of the pleura ($n = 9$, all mesotheliomas) was significantly elevated (SMR, 3.57; two-sided *p* value, 0.002). None of the other organ-specific cancers in workers monitored for plutonium occurred significantly more frequently than in national rates, and none of the rates differed significantly from those of workers who were not monitored. The lack of dosimetry for internal doses and possible confounding by exposure to external radiation weaken the reliance that can be placed on the relative absence of excess cancer rates in workers monitored for plutonium.

2.4.2 *USA*

The longest medical follow-up study of plutonium workers involved 26 white men who were exposed at Los Alamos, New Mexico, in 1944–45 while working on the Manhattan Project during the Second World War. This Project, for the design and building of the first atomic bomb, involved chemical and metallurgical research on plutonium and fabrication of plutonium-containing parts (Voelz & Lawrence, 1991; Voelz *et al*., 1997). The workers were exposed to very pure ^{239}Pu because the ^{241}Am was removed (the Am content was 2–5% of that in a comparable amount of plutonium processed in the 1980s). Inhalation of plutonium was the main pathway of exposure of these workers. Their effective doses, through 1994 or year of death, range from 0.1 to 7.2 Sv with a median value of 1.25 Sv (mean, 2.08 Sv [assuming a radiation weighting factor of 20 because of α-particle emission, see IARC, 2000). The dose of plutonium deposited by 1994 or year of death ranged from 50 to 3180 Bq, with a median value of 565 Bq (mean, 970 Bq). The doses of external radiation in 1944–45 were not measured, as no personal dosimeters were used until the end of 1945, but were believed to be low. Medical examinations and dosimetry were performed at roughly five-year intervals from 1952. The results of a study of deaths through 1994 are given in Table 45. The rate for all causes of death was significantly decreased in these workers when compared with national rates, due primarily to a low rate of death from diseases of the circulatory system. The mortality rate ratios for these workers were also compared with those of 876 unexposed Los Alamos workers hired on comparable dates. The rate ratio for death from all causes was 0.77 (95% CI, 0.36–1.6) and that from all malignant neoplasms was 1.5 (95% CI, 0.46–4.9). One bone sarcoma was observed in these workers, which originated in the sacrum and became symptomatic in 1988, about 43 years after exposure. The individual, a chemist, had received an effective dose of plutonium of 1.3 Sv, essentially the median dose for this cohort. The amount of plutonium deposited at the time of death, calculated from urinary excretion, was 580 Bq; the cumulative dose to the bone surfaces is estimated to be 0.44 Gy two years before appearance of the tumour. Three cases of lung cancer (with one death) were also observed, but among heavy smokers. Although the health of this cohort has been monitored for 50 years, the group is too small to allow precise estimates of risk.

Deaths among 5413 workers employed at the Rocky Flats, Colorado, nuclear weapons facility were investigated in order to estimate the risks from exposure to plutonium and external radiation (Wilkinson *et al.*, 1987). The cohort consisted of all white men who had been employed at this facility for at least two years between the beginning of operations in 1952 and 1979. In comparison with death rates for the USA, significantly fewer deaths from all causes, all cancers, lung cancer, circulatory system diseases and accidents, poisonings and violence were observed (see Table 46). The three deaths from cancers of the liver and gall-bladder did not result in a statistically significantly elevated SMR (1.39; 90% CI, 0.38–3.59). No bone tumours occurred in this cohort. A significant excess of benign and unspecified neoplasms was found; all

Table 45. Standardized mortality ratios (SMRs) of 'Manhattan Project' plutonium workers through 1994 in comparison with rates for white men in the USA

Cause	Observed	Expected	SMR	95% CI
All	7	16.3	0.43	0.17–0.88**
All malignant neoplasms	3	4.0	0.75	0.15–2.18
Lung cancer	1	1.5	0.68	0.01–3.79
Prostate cancer	1	0.3	3.42	0.04–19.04
Bone cancer	1	0.01	96.4	1.26–536**
All diseases of circulatory system	2	7.7	0.26	0.03–0.93*
All respiratory diseases	1	1.2	0.83	0.01–4.64
All external causes	1	1.3	0.79	0.01–4.40

From Voelz *et al*. (1997); CI, confidence interval
* One-sided *p*-value, < 0.05
** One-sided *p*-value, < 0.01

Table 46. Standardized mortality ratios (SMRs) for selected causes of death among white male workers in Rocky Flats compared with the death rates in the USA

Cause of death[a]	Observed	Expected	SMR	90% CI
All	409	656.21	0.62	0.57–0.68
All cancers	95	134.21	0.71	0.59–0.84
Lung cancer	30	46.57	0.64	0.46–0.87
Benign and unspecified (210–239)	7	1.86	3.76	1.77–7.07
All circulatory system (390–458)	193	315.02	0.61	0.54–0.69
Accidents, poisonings and violence (800–998)	55	85.11	0.65	0.51–0.81

From Wilkinson *et al*. (1987); CI, confidence interval
[a] ICD, 8th rev.

seven cases were intracranial tumours. In a case–control study of the brain tumours at Rocky Flats (Reyes *et al*., 1984), no statistically significant association was found with exposure to either external radiation or plutonium. Plutonium-exposed workers at Rocky Flats were defined as those employees with plutonium deposits ≥ 74 Bq, the detection limit of the urine bioassays. The mortality rates of plutonium-exposed workers were compared with those of unexposed workers (< 74 Bq) after a 2-, 5- and 10-year lag. The rate ratios for only two categories — all causes of death and all lymphatic and haematopoietic neoplasms combined — were significantly increased on the basis of 90% confidence intervals. The rate of all causes of death was increased with a 5-year lag (n = 74; rate ratio, 1.33; 90% CI, 1.05–1.68) and a 10-year lag

(*n* = 40; rate ratio, 1.39; 90% CI, 1.04–1.87). The incidence of all lymphatic and haematopoietic neoplasms combined (*n* = 4) was elevated with a 2-year lag (rate ratio, 7.69; 90% CI, 0.99–72.93) and a 5-year lag (*n* = 4; rate ratio, 9.86; 90% CI, 1.26–94.03). The four neoplasms in this combined category were all of different cell types: lymphosarcoma (reticulum-cell sarcoma), non-Hodgkin lymphoma, multiple myeloma and myeloid leukaemia. It seems unlikely that these different diseases are related biologically, although they are commonly grouped in studies of limited numbers of cases. The small number of cases in this study (four or fewer in each organ-specific category) resulted in wide confidence intervals and limited the precision of results. In trend analyses with individual doses from external radiation and deposited plutonium independently, no overall dose–response relationship was found.

A cohort study was conducted through 1990 of deaths among 15 727 white men who had been employed by the Los Alamos National Laboratory during 1943–77. The laboratory has been an important nuclear weapons research and design laboratory since the Second World War (Wiggs *et al*., 1994). Mortality rate ratios were calculated for 303 plutonium-exposed workers, defined as persons with internal deposition of plutonium ≥ 74 Bq, in comparison with 3472 unexposed workers monitored for plutonium (< 74 Bq); plutonium deposits measured after 1980 were not included in the analysis because a 10-year tumour induction period for plutonium was assumed. The rate ratios for deaths from all causes and all cancers were close to 1.0. No statistically significant increases or deficits in rate ratios were observed. The rate ratio for lung cancer (eight cases in plutonium-exposed persons) was 1.78 (95% CI, 0.79–3.99). One case of osteogenic sarcoma was observed among the plutonium-exposed workers. The characteristics of this case, described by Voelz and Lawrence (1991), are discussed above.

The studies conducted in the United Kingdom and the USA on plutonium workers provide no evidence of excess risks of either lung cancer or liver cancer. One bone cancer in a plutonium-exposed person was identified in these studies, and its causation should remain questionable until confirmatory evidence of risk to the bone is obtained from other studies. As these studies have limited power, they provide little convincing evidence that the exposure to plutonium at relatively low levels experienced in these occupational settings is associated with an increased risk for cancer.

2.4.3 *Russian Federation*

The first Russian nuclear complex is now known as the Mayak Production Association. It is located in the southern Urals, about 100 km from Chelyabinsk (now called Ozyorsk) (Koshurnikova *et al.*, 1997a). This nuclear complex, which included an industrial nuclear (uranium–graphite) reactor, a plant for radiochemical separation of plutonium from irradiated nuclear fuel in the reactor (radiochemical plant) and a plant for the production of standard plutonium (plutonium production plant), was put into operation between June 1948 and March 1949. There are two other nuclear complexes

in the Russian Federation (near Tomsk and Krasnoyarsk), in which workers could be exposed to plutonium, but no data were available on health effects in these workers.

Clinical studies and studies of working conditions were begun at Mayak practically at the inception of its operation; however, because of the regime of secrecy, the results of these studies were summarized as classified reports or were published in classified journals. The first publication available in the open literature, which described working conditions, levels of exposure to radiation and some early and late health effects, appeared only in 1990 (Nikipelov *et al*., 1990). This paper provides information on mortality from cancer among workers who had started working at Mayak between 1948 and 1958. The paper also mentioned for the first time that the cancers in the Mayak workers might have been induced not only by external exposure to γ-radiation but also by internal exposure to deposited plutonium. Although this paper does not provide evidence for the carcinogenicity of plutonium, it was a catalyst for subsequent publications directly relevant to the carcinogenic effects of plutonium and for declassification of papers published earlier in the classified journals.

Studies on the metabolism and dosimetry of plutonium and the health effects of exposure to this element were conducted at Branch No. 1 of the First Institute of Biophysics (FIB-1). The distribution of plutonium in the human body was found to be highly non-uniform, regardless of the route of intake, although after inhalation it was deposited mainly in the lung, liver and skeleton. Post-mortem radiometry showed that the distribution of inhaled plutonium compounds in the human body was determined by its physical and chemical properties (Plotnikova, 1965; Khokhryakov & Kudryavtseva, 1985; Khokhryakov *et al*., 1990, 1998). On the basis of 34 autopsies, Plotnikova (1965) showed that larger amounts of inhaled soluble plutonium compounds were transferred from the lung to the skeleton than to the liver, while most of the plutonium in insoluble compounds was retained in the lung. On the basis of post-mortem radiometry for 177 cases, Khokhryakov and Kudryavtseva (1985) and Khokhryakov *et al.* (1990) studied the distribution and secondary deposition in various organs of plutonium absorbed into the bloodstream. They showed that, regardless of the solubility of inhaled compounds, extrapulmonary plutonium accumulated mainly in the skeleton (about 60%) and liver (about 30%). Khokhryakov *et al.* (1998) reported that retention of plutonium in the lung varied over time, was strongly dependent on the solubility of inhaled aerosols and represented about 2.5% of the total body burden of soluble compounds and 23% of the burden of plutonium compounds with low solubility.

Since studies in both humans and experimental animals show that inhaled plutonium is deposited mainly in the lung, liver and bone, studies were conducted at the FIB-1 to evaluate the risks for cancer in these organs.

(*a*) *Lung cancer*

Cases of lung cancer among Mayak workers who were exposed to plutonium were described in the early 1970s (Yakushina *et al.*, 1972; Koshurnikova *et al*., 1973), and lung cancer incidence was first studied by Moroz (1976). The incidence in workers

who received cumulative doses of external γ-radiation higher than those permissible at the time (most received doses > 100 roentgen [about 1 Gy] and > 0.02 μCi [740 Bq] plutonium to the lung) 20 years after the beginning of exposure was significantly higher than that in workers exposed to the same types of radiation within permissible dose limits or in those who had never worked at Mayak.

Since that time, three epidemiological studies have been conducted at FIB-1: a cohort study by the epidemiology department, a cohort study by the internal dosimetry laboratory and a case–control study by the clinical department. These studies are based on partially overlapping material.

(i) *Cohort study by the epidemiology department*

In the study by the epidemiology department, mortality was followed-up for about 19 000 male and female workers (Table 47) who had been hired at the nuclear reactor and radiochemical and plutonium production plants between 1948 and 1972 (regardless of duration of employment). The number of subjects in the cohort varied slightly over time as details of occupational histories became available and duplicate records were found. The findings have been reported for successive follow-up intervals. The most detailed description of the cohort is that of Koshurnikova *et al.* (1999). Vital status was ascertained in address bureaus and in some cases from relatives of the cohort members; the fact of death was obtained from the address bureau and the cause of death from vital statistics departments. As of 31 December 1994, 90% of the cohort had been traced, and the cause of death was known for 97% of the deceased cohort members. Cause of death was determined from death certificates (45%), autopsy records (43%), other medical documents (5%) and reports from relatives (7%). Workers in all the facilities were exposed to external γ-radiation, and those in the radiochemical and plutonium production plants had potential internal exposure as a result of inhalation of plutonium aerosols. For the analysis, those who had worked at more than one Mayak plant were assigned to one plant according to the following scheme: plutonium production plant:

Table 47. Numbers of workers by sex, period of hire and plant at the Mayak nuclear complex, Russian Federation

Plant	Sex	Period of hire				Total
		1948–53	1954–58	1959–63	1964–72	
Reactor	M	1757	643	609	436	3445
	F	672	154	66	77	969
Radiochemical	M	2339	1741	1227	584	5891
	F	1329	289	243	158	2019
Plutonium production	M	1467	980	1309	986	4742
	F	910	238	311	305	1764

From Koshurnikova *et al.* (1999)

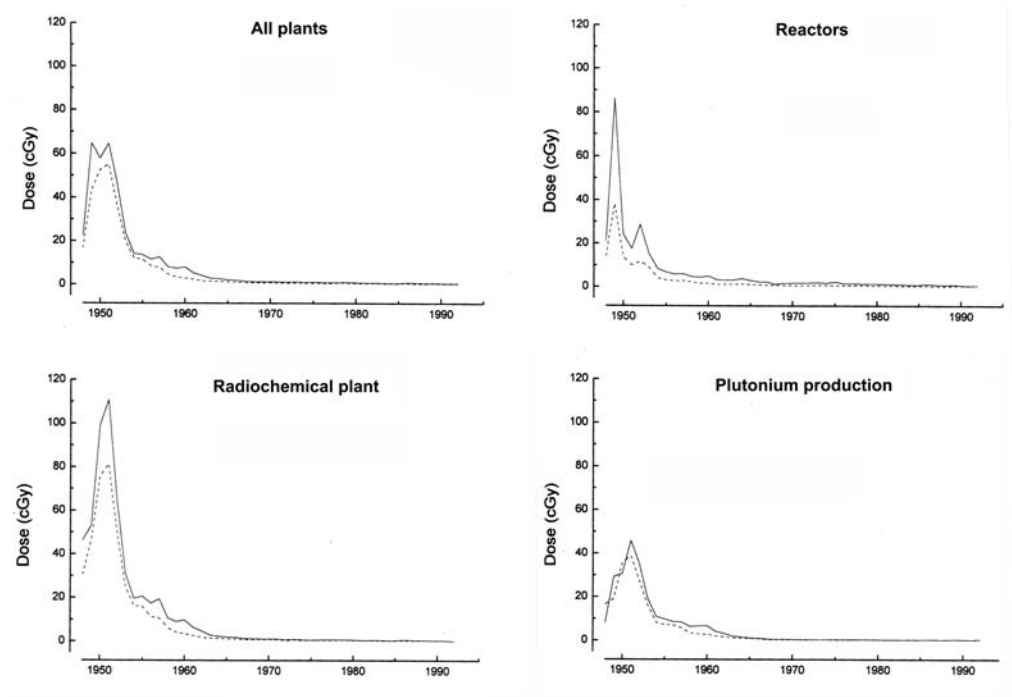
ever worked in the plutonium production plant; radiochemical plant: ever worked in the radiochemical plant and never in the plutonium production plant; nuclear reactors: worked only in nuclear reactors. The assignment was based on the degree of occupational exposure to plutonium. Working conditions at the plutonium production plant were considered to be the most unfavourable because of the highest potential exposure to plutonium.

Individual monitoring for exposure to external radiation at Mayak was conducted from the inception of operations of the main Mayak plants in 1948, when the Radiation Safety Department began to keep individual film-badge measurements of external γ-radiation doses. About 83% of the workers in the study cohort had been monitored. In general, workers were not monitored when they were considered to have little or no likelihood of external exposure. The highest doses of external γ-radiation were received by the workers in the late 1940s to early 1950s, many of the cumulative doses exceeding 1 Gy. From the mid-1950s, the annual doses decreased considerably. Workers assigned to the radiochemical plant had the heaviest exposure to external γ-radiation (Figure 8). During 1948–53, dosimeters were changed for each working shift. By 1953, the daily doses were considerably reduced, and workers were placed on weekly or, in some departments, monthly exchange schedules. By 1960, dosimeters were changed monthly in almost all departments. The body burden of plutonium and doses from deposited plutonium were estimated at the FIB-1 dosimetry laboratory. The algorithm for estimating plutonium content and dose developed at this laboratory was approved as an obligatory standard for all nuclear industry plants in the Russian Federation. The body burdens of Mayak workers were evaluated by this method from measurements of plutonium in urine from the late 1960s. Thus, only about 30% of the cohort members with potential exposure to plutonium (radiochemical and plutonium production plant workers) were monitored for plutonium body burden according to the standard method.

Mortality from lung cancer was analysed only for workers who were hired during the first decade of operations at Mayak (1948–58) (Koshurnikova *et al*., 1992, 1996, 1997a,b, 1998), when there was extensive exposure to external γ-radiation and high concentrations of plutonium aerosols in the air of the working premises. The average cumulative whole-body dose of external γ-radiation of workers who started work during this period was 1.28 Gy for men and 1.11 Gy for women. The average dose of internal α-particle radiation to the lung for workers with a measured plutonium body burden was 6.56 Sv for men and 12.61 Sv for women, assuming a radiation weighting factor of 20 for plutonium as an α-particle emitter (Koshurnikova *et al*., 1997a). As only limited information was available on smoking (ever/never), mortality from lung cancer was analysed separately for men (most of whom were smokers at the time of the study) and women (mostly non-smokers).

Koshurnikova *et al.* (1998) analysed mortality from lung cancer during 1948–93 among 1479 male workers with an average dose of external γ-radiation of 1.78 Gy and an average equivalent dose to the lung from plutonium of 6.56 Sv, of known vital

Figure 8. Average annual doses of external γ-radiation in the Mayak nuclear complex by year and plant



From Koshurnikova *et al.* (1999). Solid lines, men; dashed lines, women

status, who had started working at the radiochemical and plutonium production plants in 1948–58 and who were examined for their body burden of plutonium. The equivalent dose to the lung (radiation weighting factor, 20) accumulated from the time of the first occupational contact with plutonium to the end of follow-up or to the date of death was used as a measure of exposure to plutonium. The expected number of deaths was calculated on the basis of age-specific lung cancer mortality rates for men in the Russian Federation averaged over the period 1970–86 and in comparison with an 'internal control group'. This comprised 3333 individuals of known vital status who had started work at the same plants during the same period and met the following criteria: average external γ-radiation dose over 20 years did not exceed the maximum permissible dose of 0.05 Gy/year (average external γ-radiation dose, 0.38 Gy), and the body burden of plutonium did not exceed the maximum permissible value of 1480 Bq (average equivalent dose to the lung from plutonium, 0.13 Sv). [The Working Group noted that exposed persons in this study had a body burden of plutonium of 1480 Bq, a level rarely exceeded by workers employed in the United Kingdom or the USA.] Since the workers included in the Mayak cohort were exposed not only to plutonium but also to external γ-radiation, an additional comparison group was used in the

analysis which consisted of workers at the nuclear reactors (1841 individuals of known vital status) who were exposed to external γ-radiation (1.02 Gy) but not to plutonium. The person–years of the cohort were calculated from 1970 (the year in which systematic monitoring of plutonium body burden was begun) and those of the comparison cohorts from the year of hire. The number of lung cancer deaths observed in the cohort was 105, and the expected numbers calculated from national statistics and for the internal control group were 42.18 and 40.67, respectively. The risk for lung cancer increased with the total dose of α-particles to the lung (Table 48). [Since the results based on national statistics and those based on the internal control group were similar, only the former are given here.] The rate of death from lung cancer was not increased among workers at the nuclear reactors when compared with the national average (47 observed versus 56.23 expected deaths), and no association was detected between death from lung cancer and the whole-body dose of γ-radiation.

A significantly elevated rate of mortality from lung cancer over the national average was also reported by Koshurnikova *et al*. (1997a) among 666 women hired at the radiochemical and plutonium production plant in 1948–58 and examined for their body burden of plutonium (Table 49). The person–years of the study group were computed from 1970. The end of follow-up was 31 December 1993. The expected numbers of deaths were calculated from age-specific rates in the Russian Federation averaged over the period 1970–86 (Koshurnikova *et al.*, 1998). The number of observed cases (15) was significantly higher than that expected (2.57), and the risk for cancer mortality was associated with the total dose of α-radiation to the lung. Most of the deaths occurred among workers with the highest equivalent dose of α-particles to the lung (> 100 Sv).

[The Working Group noted that the analyses described above have the following limitations: no adjustment for the possible effects of γ-radiation and smoking, although there was little evidence in the cohort of an independent effect of long-term exposure to γ-radiation on lung cancer risk; the dose of α-particles was not treated as a time-dependent variable; and secular changes in the baseline rates were not explicitly accounted for in the analysis. In addition, the possible contribution of neutrons was not estimated. Furthermore, the dose to the lung was averaged over the entire lung whereas in fact the dose distribution was inhomogeneous. Computation of person–years in the study cohort from 1970 might lead to underestimation of person–years, as would exclusion of person-years for people lost to follow-up. In contrast, assignment of workers who had worked at more than one plant to the ‘most dangerous’ plant might have led to overestimation of the person–years for the plutonium production plant and underestimation of the person–years for the nuclear reactor plant.]

Kreisheimer *et al*. (2000) analysed mortality from lung cancer among men in the same cohort hired during 1948–58 and employed in plutonium and reprocessing plants for a longer follow-up period (1948 to end of 1995). The analysis differed from that of Koshurnikova *et al*. (1998): the dose of α-particles from plutonium and the external dose of γ-radiation were treated as time-dependent variables and the baseline

Table 48. Mortality from lung cancer in men in the Mayak nuclear complex as a function of α-particle dose to the lung

	Equivalent dose (Sv, assuming radiation weighting factor of 20)										
	< 0.5	0.5–1.7	1.8–3.9	4.0–6.9	7.0–12.9	13.0–19.9	20.0–29.9	30.0–59.9	60.0–119	≥ 120	Total
Average dose (Sv)	0.27	1.03	2.75	5.36	9.51	16.17	24.64	39.9	81.35	260.7	6.56
Persons	360	474	268	143	89	45	45	28	18	9	1479
Person–years[a]	7875	10 482	5716	3104	1807	999	856	465	275	114	31 693
Observed lung cancer deaths	13	14	13	11	12	9	13	7	8	5	105
Expected deaths	9.47	14.01	7.97	4.43	2.43	1.37	1.24	0.7	0.42	0.14	42.18
SMR (95% CI)	1.37 (0.60–3.13)	1.0 (0.48–2.07)	1.63 (0.69–3.88)	2.48 (0.84–7.29)	4.95 (1.28–19.04)	6.25 (1.14–37.59)	10.51 (1.74–63.4)	9.95 (0.91–109.0)	19.07 (0.92–396)	34.8 (0.2–∞)	2.49 (1.75–3.53)
SR (cases per 10^5 person–years)	99.4 ± 35.5	72.4 ± 26.3	118.2 ± 45.4	179.6 ± 76.0	358.1 ± 140.5	474.3 ± 217.4	760.8 ± 297.0	720.0 ± 392.1	1380.3 ± 703.6	2520 ± 1468	180.2 ± 23.8

From Koshurnikova *et al.* (1998). SMR, standardized mortality ratio; CI, confidence interval; SR, standardized rate. Expected numbers of deaths calculated on the basis of national statistics. The mortality rate for all people over 20 combined was 72.4 cases per 10^5 person–years.

[a] Person–years were calculated from 1970, when systematic monitoring of workers for plutonium body burden by urinary excretion was begun.

Table 49. Mortality from lung cancer among women in the Mayak nuclear complex in whom the body burden of plutonium was measured

Deaths	Average equivalent dose (Sv)[a]			
	1.2	8.3	116.2	Total (12.5)
Observed	2	3	10	15
Expected	0.90	0.49	0.18	2.57
Observed/expected	1.05	6.13	55.7	5.84*

From Koshurnikova *et al*. (1997a)
* Significant ($p < 0.05$)
[a] Dose of α-particle to the lung with a radiation weighting factor of 20

rate of death from lung cancer was not taken from national statistics but from the cohort itself. For both α-particles and γ-radiation, the results of the analysis are consistent with linear dose-dependence. The estimated excess relative risk per unit organ dose equivalent in the lung due to plutonium α-particles at age 60 was equal to 0.6/Sv (95% CI, 0.39/Sv–1.0/Sv), with a radiation weighting factor of 20 for α-particles. For the γ-radiation component, the analysis suggested an excess relative risk for death from lung cancer at the age of 60 of 0.20/Sv, but the confidence interval was very wide (from –0.04/Sv to 0.69/Sv).

(ii) *Cohort study by the internal dosimetry laboratory*

Another cohort study was conducted at the FIB-1 internal dosimetry laboratory (Khokhryakov *et al*., 1988; Khokhryakov & Romanov, 1992, 1994, 1996; Khokhryakov *et al*., 1998). Khokhryakov and Romanov (1992, 1994) reported the findings for the period 1970–89 for the cohort of 2346 workers (1832 men, 514 women) and 45 deaths from lung cancer. Later reports (Khokhryakov & Romanov, 1996; Khokhryakov *et al*., 1998) were based on a cohort consisting of 4279 workers (3316 men, 963 women or 3309 men, 970 women) followed during 1970–89 and 80 lung cancer deaths. [The Working Group noted that the criteria for inclusion in the cohort and procedures for determining vital status and cause of death were not described.]. The mean dose of γ-radiation to the lung of these workers was 0.9 Gy, and the mean dose of total α-particles was 0.15 Gy (3 Sv) (Khokhryakov *et al*., 1998). The computations were not aimed at separating the effects of γ-radiation and α-particles. Information on smoking was not available. The analyses were based on the constant relative risk model with a least-squares fit to the cumulative incidence in calendar years. Estimates of the expected number of death were based on age- and sex-specific mortality rates in the former USSR in 1986. Secular changes in the baseline rates were not considered in the analysis.

Khokhryakov and Romanov (1996) reported 80 lung cancer deaths, while 48.17 were expected (31.83 excess deaths). All the excess deaths were concentrated in the dose category > 4.0 Sv (Table 50). For doses < 4 Sv, the authors found fewer lung cancer deaths than expected, which indicated to them that the 'spontaneous' rate of lung cancer in the study cohort was lower than the national average rate, perhaps due partly to a 'healthy worker' effect. In order to account for the difference between the 'spontaneous' lung cancer rate in the study cohort and the national average, the authors introduced the ratio of the two, estimated to be 0.229. Introduction of this parameter increased the estimate of the number of excess ('radiation-induced') lung cancers to $80 - 48.17 \times 0.229 = 68.97$. Khokhryakov *et al.* (1998) investigated the effect of the choice of the numerical fitting procedure on the results. The estimates of the number of 'radiation-induced' lung cancers were high with all the procedures, being in the range 49.9–66.42 depending on the procedure chosen.

Table 50. Expected and observed numbers of deaths from lung cancer by dose among workers at the Mayak nuclear complex

	Equivalent dose category (Sv)[a]				
	0–0.25	0.25–1.00	1.00–4.00	> 4.00	All
No. of exposed	1119	1001	1302	857	4279
Observed cases	1	5	16	58	80
Expected cases	5.23	8.87	18.1	16.0	48.2
Ratio	[0.19	0.56	0.88	3.63	1.66]
95% confidence interval	[0.02–1.65	0.19–1.71	0.45–1.74	2.07–6.34	1.16–2.38]

Adapted from Khokhryakov and Romanov (1996). Ratio and 95% CI calculated by the Working Group. Doses were calculated to 31 December 1989 or the time of death. Expected numbers were calculated on the basis of age-specific lung cancer mortality rates for the urban population of the former USSR during 1986.

[a] A radiation weighting factor of 20 was applied.

(iii) *Case–control study by the clinical department*

The results of the case–control study of lung cancer in Mayak workers conducted at the FIB-1 clinical department have appeared in several publications (Tokarskaya *et al.*, 1993, 1994, 1995, 1996a,b, 1997a,b). The cases were those of individuals who had ever worked at the main plants of Mayak and who developed histologically confirmed lung cancer between 1966 and 1991 (162 persons: 148 men and 14 women). The controls (338 persons: 296 men, 42 women), matched for sex, year of birth (± 5 years), year of hire (± 2 years), occupation and workplace (department, sector), were workers at the same plants who did not develop lung cancer during this period. Quantitative data on smoking were obtained by direct interviews conducted by medical experts on the basis of a standard questionnaire. A smoking index (product of the number of years of

smoking and the average number of cigarettes smoked daily) was used. Data on previous pulmonary disease were abstracted from medical documents. Estimates of the body burden of plutonium and the dose to the lung from deposited plutonium were provided by the FIB-1 internal dosimetry laboratory. Data on the doses of external γ-radiation measured from film badge dosimeters were provided by the Mayak Radiation Safety Department. Odd ratios were calculated by logistic regression, and univariate analysis was used to estimate crude odds ratios. Multiple logistic regression with stepwise selection of independent variables based on the maximum likelihood method was used for multivariate analysis. The odds ratio for each variable was adjusted for all other variables. Tokarskaya *et al.* (1994, 1995) evaluated 11 potential risk factors for lung cancer and identified six significant ones. One was plutonium deposition in body. In later reports, Tokarskaya *et al.* (1996a, 1997a) evaluated the three most important factors: smoking, plutonium deposition and external γ-radiation (Table 51). The dose–response relationship was evaluated in terms of plutonium body burden, absorbed dose of plutonium to the lung and equivalent dose of external and internal radiation. Both the crude and the adjusted odds ratios were significantly elevated in the two highest ranges of exposure, whether exposure was expressed as plutonium level or total exposure (Table 51). For γ-radiation, the crude odds ratios were elevated at doses > 2 Gy, but, after adjustment, none of the odds ratios was statistically significant. There was a strong association between lung cancer and smoking, both the crude and the adjusted odds ratios being significantly elevated with smoking indices above 0. [The Working Group noted that the case–control analysis confirmed the finding that high doses of plutonium cause lung cancer, and the attempt to control for the strong effect of smoking was important. However, the shapes of the dose–response curves in the cohort and the case–control analyses differed. One possibility is that the findings in the cohort study were confounded by smoking, but since the analysis was primarily of men, it seemed unusual to expect that smoking history might vary by plutonium dose. Another possibility in the case–control study is that the lung doses of female workers were much higher than those of males, whereas virtually all of the male patients and only one of the female patients were smokers. Khokhryakov *et al.* (1998) suggested that the curvilinearity in the dose–response curve in the case–control study may be an artefact due to combining two subgroups with different characteristics, whereas the cohort findings are based exclusively on data for men. Other methodological concerns include the possibility of overmatching in the case–control analysis, i.e. the controls were matched to cases on calendar year of hire, occupational title and workplace (shop, sector), essentially forcing the potential plutonium exposure to be similar. The possible distorting effect of matching dead cases mainly with living controls was also noted.]

(iv) *Cancer location and histopathological analysis*

Attempts were made to determine whether the lung cancers found in plutonium-exposed individuals had specific characteristics. A number of reports describe the location within the lung and the distribution by histological type of the lung cancers

Table 51. Dependence of the risk for lung cancer on the values of various risk factors among workers at the Mayak nuclear complex

Factor	Value		Frequency		Crude odds ratio	Adjusted odds ratio		Trend	
	Range	Mean	No. of cases (cancer)	No. of controls		Point estimate	95% confidence interval	χ^2	*p*
^{239}Pu body burden (kBq)	0–0.148	0.01	44	86	1.0	1.0			
	0.149–0.59	0.34	16	52	0.60	0.56	0.28–1.12	4.9	< 0.05
	0.60–2.29	1.18	28	97	0.56**	0.59*	0.32–1.04		
	2.30–8.99	4.2	24	71	0.66	0.83	0.45–1.57		
	9.0–35.6	16.5	33	30	2.15**	2.48**	1.28–4.82	16.1	< 0.001
	35.7–140.6	54.2	17	2	16.6**	59.3**	11.2–314		
Absorbed lung dose (Gy)	0	0	31	69	1.0	1.0			
	0–0.10	0.042	48	118	0.91	0.84	0.45–1.5	2.9	< 0.1
	0.11–1.0	0.353	33	116	0.63**	0.71	0.39–1.3		
	1.01–2.0	1.38	13	18	1.6	2.0	0.80–5.0		
	2.01–5.2	3.30	21	15	3.1**	3.7**	1.60–8.7	10.3	< 0.01
	5.21–17.0	9.70	16	2	17.8**	96.0**	16.2–571		
Summary equivalent dose to the lung (Sv)[a]	0–0.8	0.31	27	59	1.0	1.0			
	0.81–6.0	2.91	60	167	0.79	0.75	0.45–1.4	1.1	> 0.1
	6.1–20.0	10.2	24	73	0.72	0.76	0.38–1.5		
	20.1–50.0	31.4	19	26	1.6	1.83	0.83–4.3		
	50.1–107	73.2	14	11	2.8**	4.0**	1.43–11	12.7	< 0.001
	108–344	187	18	2	19.7**	65.3**	13.5–317		

Table 51 (contd)

Factors	Value		Frequency		Crude odds ratio	Adjusted odds ratio		Trend	
	Range	Mean	No. of cases (cancer)	No. of controls		Point estimate	95% confidence interval	χ^2	p
Total γ-radiation (Gy)	0–1.0	0.30	62	168	1.0	–	–		
	1.01–2.0	1.42	40	77	1.4	–	–		
	2.01–4.0	2.70	56	88	1.7**	–	–		
	4.01–9.99	5.40	4	5	2.2*	–	–		
Smoking index	0	0	14	93	1.0	1.0			
	1–500	300	41	94	2.9**	5.36**	2.2–12.8	27.7	< 0.001
	501–2000	930	107	151	4.6**	9.35**	4.1–21.4		

From Tokarskaya *et al*. (1997a)
* ($p < 0.1$)
** ($p < 0.05$)
[a] From internal α- and external γ-radiation

in Mayak workers (Koshurnikova & Nifatov, 1978; Tokarskaya *et al.*, 1993; Koshurnikova *et al.*, 1995; Tokarskaya *et al.*, 1995, 1996b).

Tokarskaya *et al.* (1993) studied the distribution of lung cancers by lobe in 131 male workers at Mayak and in 178 men who had never worked at Mayak. As the average age of the study group (56.7 years) was lower than that of the control group (61.7 years), an additional, smaller control group (97 subjects) of an average age of 56.3 years was used. Of the 131 Mayak workers, 24 were exposed only to external γ-radiation (average dose, 0.58 Gy) and constituted an additional control group. Only 1% of the study subjects had never smoked, 14% had stopped smoking more than five years previously, and 85% were current smokers. The study and control cases were examined in the same pathology laboratory. The authors noted that the lung cancers in the study subjects were located in the lower lobe more frequently (45%) than in either of the control groups (25%), although the lung content of plutonium is higher in the upper lobe of the lung (Plotnikova, 1965).

Tokarskaya *et al.* (1995, 1996b) described the distribution of lung cancers by histological type in Mayak workers (168 cases: 154 men, 14 women) and in unexposed population controls (157 control cases: 144 men, 13 women). All the cases (both study and control) occurred between 1966 and 1991, and the age range was similar. The study cases were divided into two groups, consisting of 125 cases in workers with a plutonium body burden of ≤ 11.0 kBq, and 43 workers with a plutonium body burden of > 11.0 kBq. All cases were examined histologically at the same laboratory. In doubtful cases, the histological type was determined by two or three pathologists at the laboratory. Histological types were classified in the WHO classification (WHO, 1982). The percentage of adenocarcinomas was higher in the workers (46%) than in the unexposed population (33%) (Table 52), and the highest percentage of adenocarcinomas (74%) was found among workers with plutonium body burdens of > 11.0 kBq.

Table 52. Distribution of histological types of lung cancer in exposed and unexposed workers at the Mayak nuclear complex

Histological type	Unexposed population (control)	Exposed workers		
		Group 1 (≤ 11.0 kBq)	Group 2 (> 11.0 kBq)	Total
Adenocarcinoma	52 (33%)	46 (37%)	32 (74%)	78 (46%)
Squamous-cell	54 (34%)	42 (34%)	5 (12%)	47 (28%)
Small-cell	36 (23%)	29 (23%)	3 (7%)	32 (19%)
Large-cell	15 (10%)	8 (6%)	3 (7%)	11 (7%)
Total	157	125	43	168

From Tokarskaya *et al.* (1995, 1996b)

Tokarskaya *et al.* (1995, 1996b) also evaluated the associations between different histological types of lung cancer and a number of radiation- and non-radiation-related factors. They reported that plutonium-related factors were most strongly associated with adenocarcinoma: the adjusted odds ratio for plutonium deposition was 4.0 (95% CI, 2.1–7.6) and that for plutonium-associated pulmonary sclerosis was 2.9 (95% CI, 1.0–8.4). The authors indicated that the latter condition was highly correlated with the level of plutonium deposition and that it was difficult to discriminate between the effects of these two factors. By excluding pulmonary sclerosis from the model, they obtained an adjusted odds ratio for plutonium deposition of 6.9, (i.e. the sum of the odds ratios for the two variables). The adjusted odds ratios for smoking and exposure to external γ-radiation were 4.3 (95% CI, 1.9–9.9) and 1.9 (95% CI, 0.99–3.5), respectively. For squamous-cell carcinoma, the association with plutonium-related factors was weaker. The adjusted odds ratio for plutonium deposition was 4.2 (95% CI, 1.4–12.8), and the association with pulmonary sclerosis was not statistically significant. The adjusted odds ratio for smoking was 6.8 (95% CI, 1.2–39).

Koshurnikova and Nifatov (1978) evaluated autopsy records for Mayak workers who had died over a period of 27 years. The records were divided into two groups: those of 408 deceased individuals (341 men, 67 women) who had been exposed to plutonium and external γ-radiation, and those of 337 individuals (290 men, 47 women) who had been exposed only to γ-radiation. The number of lung cancer deaths was 31 in the first group and 15 in the second, and the percentage of cancers located in the lower lobe of the lung was 29% in the first group and 13% in the second. The percentage of adenocarcinomas was higher in the first group (42%) than in the second group (27%). Koshurnikova *et al.* (1995) studied the distribution by histological type of lung cancers that occurred in workers at the radiochemical and plutonium production plants and in workers at the nuclear reactors. They found that the proportion of adenocarcinomas was higher among workers at the radiochemical and plutonium production plants (43.3%) than among reactor workers (23.8%); however, the percentage of adenocarcinomas in the control group of workers exposed to external and internal radiation within the radiation protection limits was almost as high as that in the radiochemical and plutonium plants workers (40.8%). [The Working Group noted that the numbers of histologically confirmed cases, on which the percentages are based, are not listed in the paper.] The authors also reported that the degree of differentiation of lung cancer was dose-dependent: poorly differentiated adenocarcinomas were diagnosed in individuals exposed to doses to the lung of > 10 Sv (a radiation weighting factor of 20 was used), while highly differentiated adenocarcinomas were diagnosed in individuals with an average dose to the lung of 2.35 Sv. Poorly differentiated squamous-cell carcinomas developed after a dose to the lung of 6.9 Sv and highly differentiated keratinizing squamous-cell carcinomas after a dose of 0.4 Sv. [The Working Group noted that no numbers were provided to support these statements.]

(*b*) *Bone tumours*

A case of osteosarcoma in a female worker at the plutonium production plant was described in 1964 by Z. Bukhtoyarova [cited by Pesternikov *et al*. (1972)]. The tumour was detected in the rib and femur 12 years after the first exposure to plutonium. The plutonium content estimated *post mortem* was 7.25 μCi [268.3 kBq] in the body and 5.61 μCi [207.6 kBq] in the skeleton. The dose to the rib was estimated to have been 320 rad [3.2 Gy], that to the spongy bone of the femur metaphysis, 204 rad [2.04 Gy], and that to the compact bone of the femur, 307 rad [3.07 Gy]. Another case was described by Pesternikov *et al.* (1972) in a woman who had worked at the plutonium production plant for nine years and who had been exposed to both soluble and relatively insoluble plutonium compounds. The woman had left her job after pulmonary sclerosis was diagnosed, and the tumour in the rib was diagnosed 11 years after the end of occupational exposure and 20 years after the first exposure to plutonium. The tumour was described histologically as a combination of a spindle-cell sarcoma and a malignant 'osteoblastoclastoma' [perhaps a fibroblastic spindle-cell sarcoma]. The plutonium content was estimated to be 2.6 μCi [96.2 kBq] in the body and 2.2 μCi [81.4 kBq] in the skeleton, and the estimated dose to the bone was 430 rad [4.3 Gy].

A report by Koshurnikova *et al*. (1973) included the two cases described above and a newly diagnosed case. Additional information on the two cases described previously revealed that the total dose of external γ-radiation had been 3.8 Gy in the first case and 1.7 Gy in the second. In the second case, the tumour recurred 1.5 years after surgical removal, resulting in death, and was found to be a spindle-cell sarcoma. The third case occurred in a female worker at the plutonium production plant 22 years after her first occupational exposure to plutonium. The tumour was located in the upper part of the shin and was an osteoblastic sarcoma mainly of the osteolytic type. The plutonium content was 2.55 μCi [94.4 kBq] in the body and 1.9 μCi [70.3 kBq] in the skeleton, and the absorbed dose to the skeleton was 640 rad [6.4 Gy]. Histoautoradiography showed diffuse tracks of α-particles in the endosteum and bone marrow in all three cases. In the cortical bone, the tracks were oriented around haversian canals. In the third case, the remains of the old bone plates were seen in the tumour tissue, and on the autoradiograms the diffuse tracks of α-particles corresponded to these plates. Some diffuse tracks were found in the connective tissue surrounding tumour nodules. No tracks of α-particles were found in the tumour cells.

All cases of malignant bone neoplasm detected in the cohort of Mayak workers between 1948 and 1996 were summarized by Koshurnikova *et al.* (2000). The authors based their analysis on the cohort of about 11 000 workers initially employed in one of the main Mayak plants in 1948–58. The procedures for determining vital status and cause of death and the sources of information on exposure to radiation in this cohort are described in the section on lung cancer. Statistical analyses were conducted by Poisson regression methods. During 1948–96, 27 cases of malignant neoplasms (bone and soft-tissue tumours; ICD-9 codes, 170–171) occurred, 19 of which were bone and cartilage

neoplasms (16 osteosarcomas, three chondrosarcomas) coded 170; the other eight cases were soft-tissue neoplasms (ICD-9 code 171), comprising one fibrosarcoma, three synovial sarcomas and four myosarcomas. In three cases, the bone tumour was not the underlying cause of death described on the death certificate, and these three cases were excluded from comparisons with national statistics. [The Working Group noted that the high rate of autopsy of deceased Mayak workers, in contrast to national rates, makes comparisons, even when based on death certificate information, problematic because of diagnostic bias.] Finding an appropriate external control group was difficult, since age- and sex-specific mortality rates from bone cancer (ICD 170) in the Russian Federation were available only for 1990–94 and were combined with the rates for soft-tissue cancers (ICD 171). Three approaches were used. Deaths in which bone or soft-tissue cancer was given as the cause on the death certificate were compared with those expected calculated from both Russian rates (age- and sex-specific for 1990–94) and rates in the USA (age-, sex- and calendar year-specific) for the combined category of bone and soft-tissue cancer. Deaths in which bone cancer was given as the cause on the death certificate were compared with those expected calculated from bone cancer rates in the USA. Partly because of the limitations of external rates and the possibility of diagnostic bias, internal comparisons by plant, external dose and body burden were also carried out. For these analyses, deaths in which bone cancer was considered to be either the underlying or the contributing cause were included. In addition, four deaths in which soft-tissue cancer in tissue very close to the bone (three synovial sarcomas, one fibrosarcoma) was an underlying or contributing cause (one death) were included. The analyses consisted of evaluations of the effects of exposure to plutonium with adjustment for the possible effects of external dose. The excess number of cases resulting from exposure was estimated by the linear relative risk model. Analyses of the effects of exposure to plutonium were limited to cases in which the body burden had been estimated, expressed in kBq. Of 8048 radiochemical and plutonium plant workers of known vital status, 2772 were monitored for exposure to plutonium. These workers and workers in the reactor plant, who had no potential exposure to plutonium, were considered to have ‘known’ plutonium body burdens, while the remaining workers were considered to have ‘unknown’ body burdens. The distribution of workers and bone tumours by plutonium body burden and external dose of γ-radiation is shown in Table 53. With all three external comparisons, the SMRs were significantly elevated for men and women: for codes 170–171, 1.8 (95% CI, 1.2–2.6) based on Russian rates and 3.1 (95% CI, 2.0–4.6) based on rates in the USA, for ICD 170, 6.6 (95% CI, 3.9–10) based on rates in the USA. The highest risk for bone cancer was noted among plutonium plant workers, with a SMR of 2.7 (95% CI, 1.4–4.7), while the SMR for the reactor plant workers was 1.3 (95% CI, 0.5–2.9), and that for the radiochemical plant workers was 1.4 (95% CI, 0.6–2.6). The SMRs for women were more than twice those for men, due, according to the authors, to the fact that both the Russian rates and rates in the USA for women were lower than those for men. The results of the internal comparisons by plant and level of exposure are shown in Tables 54 and 55. The relative

Table 53. Numbers of workers, numbers of bone tumours and mean external dose by category of plutonium monitoring and external dose among workers at the Mayak nuclear complex

Exposure	All workers		Men		Women	
	No. of workers (bone tumours [a])	Mean dose[b] (Sv)	No. of workers (bone tumours[a])	Mean dose[b] (Sv)	No. of workers (bone tumours[a])	Mean dose[b] (Sv)
Plutonium body burden (kBq)						
Known						
0	3314 (4, 0)	0.81	2418 (3, 0)	0.93	896 (1, 0)	0.51
> 0–1.48	1297 (0, 2)	1.55	856 (0, 2)	1.48	441 (0, 0)	1.68
1.48–7.40	659 (1, 0)	1.74	495 (0, 0)	1.95	164 (1, 0)	1.10
≥ 7.40	251 (3, 0)	2.24	180 (1, 0)	2.36	71 (2, 0)	1.93
Subtotal	5521 (8, 2)	1.16	3949 (4, 2)	1.24	1572 (4, 0)	0.96
Unknown[c]						
Radiochemical	3134 (6, 0)	1.35	2262 (5, 0)	1.40	872 (1, 0)	1.22
Plutonium	2142 (6, 1)	0.40	1465 (2, 0)	0.40	677 (4, 1)	0.40
Subtotal	5276 (12, 1)	0.96	3727 (7, 0)	1.01	1549 (5, 1)	0.86
External dose[b] (Sv)						
Unmonitored	1416 (2, 0)	0.00	836 (1, 0)	0.00	580 (1, 0)	0.00
> 0, < 0.1	1182 (0, 1)	0.04	814 (0, 1)	0.04	368 (0, 0)	0.04
0.1–1	4290 (6, 0)	0.47	3093 (4, 0)	0.47	1197 (2, 0)	0.45
1–3	2955 (8, 1)	1.79	2203 (3, 1)	1.80	752 (5, 0)	1.77
≥ 3	954 (4, 1)	4.35	730 (3, 0)	4.38	224 (1, 1)	4.29
Total	10 797 (20, 3)	1.07	7676 (11, 2)	1.13	3121 (9, 1)	0.91

From Koshurnikova *et al.* (2000)

[a] The first number is the number of bone tumours indicated as the cause of death on the death certificate; the second is the number of bone tumours indicated as a contributing cause of death on the death certificate.

[b] External γ-radiation dose; the dose for the two years preceding the end of follow-up was excluded.

[c] Workers in the radiochemical and plutonium plants who had not been monitored before 1996; 493 of these workers were monitored in 1996 or later.

Table 54. Numbers of person–years and bone tumours and relative risks (with 95% confidence interval [CI]) by plant at the Mayak nuclear complex

Plant	No. of person–years (no. of bone tumours)	Relative risk[a] (95% CI)
Reactor	110 043 (4)	1.0
Radiochemical	193 421 (8)	1.2 (0.4–4.6)
Plutonium	124 036 (11)	2.4 (0.8–8.8)

From Koshurnikova *et al*. (2000)
[a] Stratified by age, calendar year and sex

Table 55. Numbers of person–years and bone tumours and relative risks (with 95% confidence interval [CI]) by category of plutonium body burden at the Mayak nuclear complex

Plutonium exposure and/or type of plant	No. of person–years (no. of bone tumours)	Relative risk[a] (95% CI)
Body burden (kBq)		
0–1.48	162 540 (6)	1.0
1.48–7.40	15 614 (1)	0.9 (0.05–5.5)
≥ 7.40	4 410 (3)	7.9 (1.6–32)
Unknown		
Radiochemical	149 878 (6)	1.4 (0.4–4.7)
Plutonium	97 058 (7)	4.1 (1.2–14)

From Koshurnikova *et al*. (2000)
[a] Stratified by age, calendar year and sex and adjusted for external dose as a linear variable

risks by plant (Table 54), not adjusted for external dose or plutonium exposure, suggest higher risks for workers in the plutonium plant. The analyses of relative risks by category of plutonium body burden, adjusted for external dose by its inclusion as a linear variable, indicated elevated risks among workers with estimated body burdens > 7.4 kBq (Table 55). The three cases of bone tumours in which the body burdens of the patients exceeded 7.4 kBq (47.8, 93.7 and 114.0 kBq) had estimated doses to the bone surface of 35, 60 and 78 Gy, respectively. An elevated risk was also found for plutonium plant workers who were not monitored for exposure to plutonium, some of whom may also have had large but unmeasured burdens. There was little evidence of an elevated risk for workers who were not monitored for plutonium in the

radiochemical plant. On the basis of the results of the external and internal comparisons, the authors concluded that the risks for bone tumours in the Mayak worker cohort were related to exposure to plutonium.

(*c*) *Liver tumours*

The first report on malignant liver tumours in Mayak workers exposed to plutonium appeared in 1978 (Migunova *et al*., 1978). The authors described three cases of liver haemangiosarcoma in female workers at the plutonium production plant (Table 56). In view of the high body burdens of plutonium, the high absorbed doses to the liver in all three cases and information from the literature on liver haemangiosarcomas in Thorotrast-treated patients (see section 2.3.2(*a*)), the authors concluded that these tumours had been induced by α-particles from deposited plutonium.

Shilnikova *et al.* (1995), in the study described in detail on the section on lung cancer, reported the mortality rate from malignant liver tumours in the Mayak worker cohort of 11 847 persons (8399 men, 3448 women) who started work at the nuclear reactor, the radiochemical plant and the plutonium production plants between 1948 and 1958. As of 1 January 1993, the vital status was known for 10 151 individuals (85.7%). Forty-eight persons had died from liver tumours (32 men, 16 women). Thirty-six of these 48 persons had worked at the radiochemical and plutonium production plants and had potential exposure to plutonium. A total of 2412 individuals (1662 men, 750 women) were monitored for plutonium: the average equivalent dose of α- and γ-radiation to the liver was 7.25 Sv for men and 11 Sv for women. For the 1888 persons exposed to doses < 7.5 Sv, the contribution of α-particles and γ-radiation was almost equal, while for the 524 persons exposed to doses > 7.5 Gy, α-particles contributed about 80% of the total equivalent dose to the liver. Eighteen deaths from liver neoplasms occurred among workers monitored for plutonium (eight men, 10 women). The expected numbers of deaths were calculated on the basis of age- and sex-specific mortality rates in the group of 9695 workers whose average annual doses were lower than those permitted at the time. [The Working Group noted that this group is not clearly defined. Since only 20% of the workers were monitored for plutonium, some individuals with a high, but unmeasured plutonium body burden might be included in this group. The annual dose of external radiation averaged over several years does not reflect the actual annual dose, which could be much higher than the maximum permissible dose in the early years of operation at the Mayak nuclear complex.]

The relative risk for liver neoplasms was significantly increased only among female workers at the plutonium production plant (Table 57). [The Working Group noted that one explanation for this finding is that women have fewer liver cancers than men.] The authors reported that female workers at the plutonium production plant had the highest doses from plutonium, with an average dose to the liver of 20.5 Sv, while the dose of male workers at the same plant was 8.8 Sv. The average doses to the liver of male and female workers at the radiochemical plant were 6.5 Sv and 5.0 Sv, respectively. These doses apply only to workers who were monitored for plutonium, who were those in jobs

Table 56. Characteristics of three cases of liver haemangiosarcomas among women at the Mayak nuclear complex

Duration of contact with plutonium (years)	Dose of external γ-radiation	Plutonium body burden	Dose to the liver from plutonium (Gy)	Age at death (years)	Time between first exposure and death (years)	Diagnosis
6	218 rad [2.2 Gy]	1.8 μCi [66.6 kBq]	5.64	57	24	Haemangiosarcoma of the liver
5	149 rad [1.5 Gy]	5.8 μCi [214.6 kBq]	5.62	46	23	Haemangiosarcoma of the liver
5	94 rad [0.94 Gy]	2.1 μCi [77.7 kBq]	5.42	49	22	Haemangiosarcoma of the liver and spleen

Data from Migunova *et al*. (1978)

Table 57. Mortality from malignant liver tumours among workers at the Mayak nuclear complex

Deaths	Sex	Plant			Total
		Reactor	Radiochemical	Plutonium production	
Observed	M	10	13	9	32
	F	2	2	12	16
Expected	M	6.90	8.73	6.29	21.9
	F	1.08	2.05	1.50	4.61
Observed/expected	M	1.45 (0.55–3.81)	1.49 (0.63–3.51)	1.43 (0.52–3.96)	1.46 (0.85–2.51)
(95% confidence interval)	F	1.86 (0.18–19.3)	0.98 (0.14–6.86)	8.01 (1.47–43.7)	3.47 (1.23–9.76)

From Shilnikova *et al*. (1995)

with the greatest likelihood of exposure to plutonium. Thus, if all the workers at the plutonium production and radiochemical plants were examined, their average doses would be lower, but the ratio of doses by sex and plant would be similar. Histological diagnoses were available for 30 of the 48 cases of liver tumours: 53% were hepatocellular carcinoma, 16.7 % were cholangiocellular carcinoma and 26.7% were haemangiosarcoma. Of the eight haemangiosarcomas, six were diagnosed in female workers. The haemangiosarcomas occurred only in persons who were exposed to plutonium. The average dose to the liver in these cases was 150 Sv.

The most recent report (Gilbert *et al*., 2000) was based on a cohort of about 11 000 workers who had started working at the Mayak nuclear complex in 1948–58. The methods of analysis used are similar to those of Koshurnikova *et al.* (2000). A total of 2207 workers (1531 men, 676 women) were monitored for plutonium and had detectable body burdens. The mean dose to the liver for these workers was 0.60 Gy (0.47 Gy for men, 0.88 Gy for women). The highest doses to the liver were received by female workers at the plutonium plant, with a mean of 1.74 Gy. The mean dose for male workers at the plutonium plant was 0.72 Gy, and those for female and male workers at the radiochemical plant were 0.24 Gy and 0.33 Gy, respectively. Sixty cases of liver tumours occurred during the period 1948–96, 13 in reactor workers, 19 in radiochemical plant workers and 28 in plutonium plant workers. In four cases, liver cancer was not recorded as the underlying cause of death on the death certificate. Since mortality rates from liver cancer in the Russian Federation were not available, comparisons were made with the incidence rates for 1990–94. Since liver cancer is nearly always fatal, the authors considered that the incidence rates should not differ greatly from the mortality rates. As the comparisons were based on incidence rates, the analyses included all liver cancers, regardless of whether they were considered to be the cause of death. [The Working Group noted that Mayak workers who died were more likely to have been autopsied and the causes to have been better diagnosed than for the general population, so that some bias due to surveillance is possible.] The internal comparisons also included all diagnoses. There was clear evidence of an excess risk for workers at the plutonium plant (SMR, 2.8; 95% CI, 1.9–3.9) and for the 23 workers with detectable plutonium burdens (SMR, 3.4; 95% CI, 2.2–5.0). The SMR for all women (n = 19) (3.0; 95% CI, 1.9–4.6) was twice that for men (n = 41) (1.5; 95% CI, 1.1–2.0). In the authors' opinion, the difference in risk between men and women might result from the larger plutonium burdens and lower baseline risks of women than of men. The authors noted that comparing mortality from liver cancer with the Russian incidence rate might have introduced bias, although they considered that bias could not explain the elevated SMRs entirely. The results of the internal comparisons also showed an excess risk for liver tumours in plutonium-exposed workers (Tables 58 and 59). The relative risks by plant (Table 58), not adjusted for external dose or exposure to plutonium, indicated an elevated risk for workers at the plutonium plant; the risk for women at this plant was higher than that for men. The analyses of relative risks by category of plutonium body burden, adjusted for external dose by including it as a

Table 58. Numbers of person–years, liver tumours and relative risks (with 95% confidence interval [CI]) by plant at the Mayak nuclear complex

Plant	All workers		Men		Women	
	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)
Reactor	110 043 (13)	1.0	80 108 (11)	1.0	29 935 (2)	1.0
Radiochemical	193 421 (19)	1.0 (0.5–2.1)	131 925 (17)	1.2 (0.6–2.7)	61 496 (2)	0.5 (0.06–4.1)
Plutonium	124 036 (28)	2.1 (1.1–4.1)	81 144 (13)	1.3 (0.6–3.0)	42 891 (15)	5.2 (1.5–33)

From Gilbert *et al*. (2000)

[a] Stratified by age, calendar year and sex

Table 59. Numbers of person–years, liver tumours and relative risks (with 95% confidence interval [CI]) by category of plutonium body burden at the Mayak nuclear complex

Plutonium body burden (kBq)	All workers		Men		Women	
	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)	Person–years (no. of liver tumours)	Relative risk[a] (95% CI)
Known						
0–1.48	162 540 (16)	1.0	112 996 (14)	1.0	49 544 (2)	1.0
1.48–7.40	15 614 (4)	1.5 (0.4–4.2)	11 278 (2)	0.9 (0.1–3.2)	4 336 (2)	7.1 (0.9–59)
≥ 7.40	4 410 (16)	17 (8.0–36)	3 159 (7)	9.2 (3.3–23)	1 252 (9)	66 (16–453)
Unknown						
Radiochemical	147 878 (10)	1.0 (0.4–2.2)	101 801 (9)	1.1 (0.5–2.6)	46 078 (1)	0.6 (0.03–6.1)
Plutonium	97 058 (14)	2.8 (1.3–6.2)	63 944 (9)	2.0 (0.8–4.8)	33 114 (5)	13 (2.4–94)

From Gilbert *et al*. (2000)

[a] Stratified by age, calendar year and sex and adjusted for external dose as a linear variable

linear variable (Table 59), indicated elevated risks among workers with estimated body burdens > 7.4 kBq; this relative risk was also larger for female than for male workers, and an elevated risk was found for female plutonium plant workers who were not monitored for exposure to plutonium. Information on histological type was available for 44 of the 60 tumours: 24 were hepatocellular carcinoma, eight were cholangiocellular carcinoma, 10 were haemangiosarcoma and two were tumours of an undifferentiated cell type. All 10 of the haemangiosarcomas occurred among workers with detectable plutonium burdens, and eight of them occurred in women. On the basis of external and internal comparisons, the authors concluded that the increased risks for liver tumours in Mayak workers were related to exposure to plutonium.

2.4.4 *Americium*

All plutonium contains some americium-241 (^{241}Am; half-life, 432.2 years), which contributes to the overall dose. It is a product of neutron interactions with ^{241}Pu that has not been totally separated from ^{239}Pu or ^{238}Pu. For example, ^{239}Pu often contains 5–15% ^{241}Am by activity. The radiation doses from ^{241}Am, if significant, are calculated separately from those of plutonium and are usually not included with the doses of plutonium in epidemiological studies. Chemically, ^{241}Am is more soluble and is transported more rapidly from wounds or the lung to the liver or bone than plutonium. Accidental exposure to essentially pure ^{241}Am has occurred, the most notable being an accident at the nuclear weapons site in Hanford, Washington, USA, involving a chemical explosion in a glove box (Toohey & Kathren, 1995). A 64-year-old chemical operator received massive percutaneous exposure to ^{241}Am from contaminated glass shards and nitric acid. A four-year intensive course of calcium trisodium diethylenetriamine pentaacetate (DTPA) and then of the zinc salt of DTPA prevented deposition in the internal organs of 99% of the ^{241}Am that entered the blood. The total amount of ^{241}Am excreted in his urine and faeces was 41 MBq (Breitenstein & Palmer, 1989). The cumulative absorbed doses to the bone, bone surface, liver and lung were 18, 520, 8 and 1.6 Gy, respectively (Toohey & Kathren, 1995). The health problems attributed to this radiation dose were thrombocytopenia and leukopenia. The man died 11 years later from pre-existing cardiovascular disease (see also section 1.2.2(i)).

2.4.5 *Summary*

Studies of plutonium workers in the United Kingdom and the USA provide little evidence that exposure to this radionuclide is carcinogenic to humans, largely because of the relatively low levels of exposure of these working populations, i.e. only a small proportion of workers had measured body burdens of plutonium > 1 kBq. In contrast, clear excesses of cancers of the lung, bone and liver were reported among Russian men and women who worked at the Mayak nuclear complex in the southern Urals. The risk was concentrated among workers who had first been employed in 1948–58 and who

had inhaled or ingested large quantities of plutonium, a significant number of workers having body burdens > 3 kBq. The estimated equivalent dose to the lung for some workers, for example, was > 80 Sv (assuming a radiation weighting factor of 20). There was little evidence that significant effects occurred at doses below about 3 kBq, but statistically significant risks were seen at the higher exposure levels. While the risks are difficult to quantify because of limitations in dosimetry and incomplete ascertainment of vital status and information on important confounders such as smoking, the demonstration of dose–response relationships for different cancer types over a broad range of doses in both men and women provides strong evidence that exposure to plutonium at sufficiently high levels is associated with an increased risk for cancer.

2.5 Uranium

Uranium is a radioactive heavy metal which occurs commonly in small amounts in all rock, soil and other natural materials. Naturally occurring uranium consists of a mixture of three radioactive isotopes, ^{234}U (0.006%), ^{235}U (0.72%) and ^{238}U (99.27%), which have half-lives of 2.4×10^5, 7.0×10^8 and 4.5×10^9 years, respectively. Natural uranium decays mainly through emission of α-particles (see Table 7 of General Remarks). The very long half-life of ^{238}U, the most abundant isotope, results in a very low decay rate per unit mass of uranium. Because of the high percentage of ^{238}U and its slow decay rate, naturally occurring uranium is, in fact, one of the least radioactive of the unstable isotopes.

Uranium is mined from natural deposits containing concentrations ranging from 0.05% to tens of per cent by mass. These deposits, called uranium ore, are typically found in sandstone formations.

Several studies have been conducted of uranium millers and of individuals involved in other uranium processing operations. Study of these individuals is often complicated by external exposures, and even in cases where there may be internal deposition, internal exposure has not always been estimated. These workers are not exposed to high concentrations of radon gas in air but may be exposed to α- and β-particles from inhaled or ingested uranium dust. Inhalation of insoluble uranium particles is the major pathway for exposure of the lung. As these studies involve persons selected for employment, their mortality rate might be expected to be lower than that of the general population (i.e. the 'healthy worker effect'. [The Working Group noted that the SMRs of an exposed cohort is about 0.7–0.9 when compared with a general population which includes some disabled or ill persons who would not be in an employed population.])

In a retrospective cohort study of mortality in 995 white men who had been employed for more than 30 days at a uranium processing facility in upstate New York, USA, between 1943 and 1949, the association between an increase in mortality rates and long-term occupational exposure by inhalation to uranium compounds was investigated (Dupree *et al*., 1987). Two comparison groups were used: the white male population of the USA and the white male populations of the New York counties of Erie and

Niagara. Vital status was known for 94.3% of the men through 31 December 1979. When the national comparison group was used, statistically significantly increased SMRs were observed for all causes of death (SMR, 1.18; 95% CI, 1.07–1.30, 429 deaths), laryngeal cancer (SMR, 4.47; 95% CI, 1.44–10.43; five deaths), all circulatory disease (SMR, 1.18; 95% CI, 1.04–1.35, 227 cases), arteriosclerotic heart disease (SMR, 1.19; 95% CI, 1.01–1.39, 159 cases), all respiratory disease (SMR, 1.52; 95% CI, 1.04–2.14, 32 cases) and pneumonia (SMR, 2.17; 95% CI, 1.26–3.47, 17 cases). No association was found with length of employment or work in the most hazardous areas of the plant. The rate of death from lung cancer was not increased (SMR, 0.97; 95% CI, 0.60–1.48, 21 cases). The internal doses from uranium were given only for the lung: 40% of the cohort received 10–100 mSv/year and 38% received > 100 mSv/year; the remainder of the cohort received < 10 mSv/year, or the value was unknown. The comparison with regional rates gave similar results.

Polednak and Frome (1981) described the mortality rates in a cohort of 18 869 white men who had been employed between 1943 and 1947 at a uranium conversion and enrichment plant in Oak Ridge, Tennessee, USA, and followed-up until 1974. Workers in certain departments (especially chemical workers) were exposed to high average air concentrations of uranium dust (up to 500 $\mu g/m^3$ of air in 1945). In comparison with mortality rates for white men in the USA, the SMRs for various causes in the entire cohort were generally < 1.00. After correction for unascertained deaths and missing death certificates, the SMR for lung cancer was 1.22 (95% CI, 1.10–1.36). Adequate data on smoking habits were not available in this study. The SMRs for various causes, including lung cancer, did not tend to be higher among 8345 workers who were employed in areas where uranium dust was present or among 4008 of these 8345 workers who were employed for one year or longer at the plant. The SMRs for other causes of death, such as bone cancer, leukaemia and diseases of the respiratory and genitourinary systems were not significantly increased. [The Working Group noted that no estimates of dose were included in the analyses.]

A retrospective cohort study was conducted among 6781 white male employees who had worked at the Oak Ridge Y-12 nuclear material fabrication plant for at least 30 days during 1947–74; vital status was determined for 6477 workers, and the cohort was followed-up until the end of 1979 (Checkoway *et al.*, 1988). Among 3490 monitored workers, the mean cumulative α-particle dose to the lung was 82 mSv (range, 0–3.1 Sv), and the mean cumulative external whole-body penetrating dose from γ-radiation was 9.6 mSv (0–4.3 Sv). When compared with the rates for white men in the USA, the mortality rates from all causes combined, cardiovascular diseases and from most site-specific cancers were decreased. Increased rates of cancers of the lung, brain and central nervous system were seen in comparison with national and State rates. Dose–response trends were detected for death from lung cancer with respect to cumulative exposure to α-particles and γ-radiation, the most pronounced trend being found for exposure to γ-radiation among workers who received ≥ 0.05 Sv of α-particles. These trends became smaller when a 10-year latency was assumed.

When no latency was assumed, the rate ratio for death from lung cancer associated with exposure to both types of radiation at ≥ 0.05 Sv compared with < 0.01 Sv was 4.60 (95% CI, 0.91–23.4), while the corresponding result when a 10-year latency was assumed was 3.05 (95% CI, 0.37–24.8). No dose–response trend in mortality from brain or central nervous system cancer was found.

The association between exposure to uranium dust and death from lung cancer was investigated among workers who had been employed for at least 183 days in any of four uranium processing or fabrication plants located in Missouri (Mallinckrodt, 1942–1966), Ohio (Fernald, 1951–1989) or Tennessee (Tennessee Eastman (same facility as studied by Polednak & Frome, 1981) and Y-12 (same facility as studied by Checkoway *et al.*, 1988), USA (Dupree *et al.*, 1995). Among workers who had potentially been followed-up for at least 30 years, 787 deaths from lung cancer were identified from death certificates. One control was matched to each case on race, sex and birth and hire dates within three years. Health physicists estimated the annual doses to the lung from exposure primarily to insoluble uranium compounds for each person on the basis of data on air concentrations or, in the case of the Y-12 workers, by urine analysis and whole-body counting. External dosimetry records were available for only 54% of the years of employment. The health physicists assigned annual external radiation doses to workers for whom personal monitoring records were available. With a 10-year lag, the cumulative doses to the lung ranged from 0 to 1.4 Gy (internal and external radiation) for cases and from 0 to 0.8 Gy for controls. Archivists collected information on smoking from occupational medical records for 48% of the cases (91% of whom were smokers) and 39% of the controls (75% of whom were smokers). The odds ratios for death from lung cancer for seven groupings of the cumulative internal dose to the lung showed no increase in risk with increasing dose. There was a suggestion of an effect of exposure for workers who had been hired at the age of 45 years or older. Further analyses with the cumulative external doses of thorium, radium and radon did not reveal a clear association between exposure and increased risk, nor did categorization of the workers by facility. In a re-analysis of workers employed at Fernald, Ritz (1999) found no significant association between risk for lung cancer and internal dose of α-particles ≥ 200 mSv, lagged by 15 years (RR, 1.92; 95% CI, 0.53–6.96).

A number of other studies have been carried out of uranium workers (Archer *et al.*, 1973; Waxweiler *et al.*, 1983; Teta & Ott, 1988; Loomis & Wolf, 1996; Frome *et al.*, 1997), but they do not provide information explicitly on the effects of internal exposure.

Some studies of workers in uranium processing plants thus showed an elevated rate of mortality from lung cancer, but the finding was not consistent in all studies. The doses to the lung were relatively low. The rates of death from cancers at other sites were increased in some studies, but the small number of cases and lack of consistency between the findings reduce their significance. [The Working Group noted that the studies of exposure to uranium are hampered by limitations in measurements of

radiation dose, potential concomitant exposure to other chemicals, possible modification of health effects with age at exposure and confounding by smoking.]

2.6 Polonium

Polonium occurs in nature as a radioactive decay product of uranium, thorium and actinium and also in tobacco smoke. The commonest natural isotope of polonium, ^{210}Po, has a half-life of 138.4 days and has an effective biological half-time of 46 days. It is a pure α-particle emitter with an α-particle energy of 5.3 MeV. It has limited industrial application. Small encapsulated sources have been used to eliminate static electricity generated in such processes as paper rolling, the manufacture of sheet plastics and the spinning of synthetic fibres. It is also used on brushes for removing dust from photographic film and in nuclear physics as a source of α-particles. Mixtures of polonium with beryllium and other light elements are used as sources of neutrons, and the greatest risk of exposure to polonium occurs during production of these sources. Roasting of phosphate ores in the manufacture of some fertilizers volatilizes the natural polonium found in these ores into an aerosol waste.

A few epidemiological studies have been conducted of workers in the United Kingdom and the USA. Beral *et al.* (1988) studied 22 552 workers who had been employed by the Atomic Weapons Establishment between 1951 and 1982. Among 9389 workers who had a record of exposure to radiation, only 638 (17%) were monitored for possible internal exposure to polonium. The incidence of cancer of the kidney (three cases) among those monitored for polonium was statistically significantly elevated ($p < 0.05$), with a SMR of 5.8 [95% CI not given]. Many workers were monitored for more than one radionuclide, and no internal doses were available to assist in interpreting this finding.

Wiggs *et al.* (1991) studied a cohort of 4402 white men employed at the Mound Facility (Dayton, Ohio, USA) during the period 1944–72, when ^{210}Po was processed and Po–Be neutron sources were manufactured. Mortality rates were evaluated by two analytical methods: SMRs with external comparison populations and a dose–response analysis with internal comparisons. The death rates of white men in the country as a whole and of white men in Ohio were used to calculate the SMRs. When the rates for all white males in the USA were used, the SMR for death from any cause among 2181 ^{210}Po-monitored workers was 0.92 (90% CI, 0.85–0.98), and that for death from any cancer was 1.01 (90% CI, 0.87–1.17). The SMRs for specific cancers were not significantly increased. That for kidney cancer ($n = 2$) was 0.63 (90% CI, 0.11–1.98), and that for all genitourinary disease was not significantly increased (SMR, 1.30; 90% CI, 0.73–2.16). The SMRs based on rates for white males in Ohio were similar. Dose–response analyses were carried out on data for men monitored for polonium by analysis of urinary excretion, according to the model recommended by the ICRP (1968). Four categories of polonium dose were used: < 10 mSv, 10–99.9 mSv, 100–999.9 mSv and ≥ 1000 mSv. In order to assess potential confounding from exposure to external

radiation, the cumulative doses of external radiation of persons in the four dose categories were assessed; no significant differences were observed. The mean external doses of radiation in the four categories ranged from 26.5 mSv to 36.1 mSv. Therefore, external ionizing radiation is not important in interpreting the results of the polonium dose–response analyses. The dose–response analyses were limited to the 2181 monitored persons for whom estimates of ^{210}Po dose were available. For two- and five-year latent periods, Mantel-Haenszel relative risks and ungrouped trend statistics were calculated for all causes, all cancers and lymphatic and haematopoietic cancers combined. No significant positive dose–response trends were observed. When a 10-year latency was used, all the cancer-specific trends were negative, except that for cancer of the pancreas, but none of the trends was statistically significant. The results of this study do not support an association between dose of ^{210}Po and mortality from any cancer or any specific cancer. [The Working Group noted that a limitation of this analysis is that measured annual doses of polonium were not available. Annual doses were assigned by evenly partitioning the cumulative dose of an individual between the dates of the individual's first and last monitoring assay, which probably resulted in misclassification of doses across person–years. The dosimetry was complex and subject to substantial uncertainty.]

2.7 Iodine

The only radionuclides that are actively absorbed in the thyroid gland are the radioiodines. The euthyroid thyroid gland absorbs 20–30% of ingested ^{131}I, but a patient with hyperthyroidism could absorb as much as 60%, and none might be absorbed after administration of stable iodine. ^{131}I is essentially a β-particle emitter, contributing 85% of the absorbed tissue dose, while the contribution of γ-radiation is 15%. This fact is used in medical practice, where radioiodines have been administered for the last 50 years in the treatment of hyperthyroidism and thyroid cancer. Radioiodines not only locally irradiate the thyroid gland but are also incorporated into thyroid hormones, thus influencing other organs of the body.

Thyroid cancers can be classified into differentiated thyroid cancers (papillary, follicular and medullary) and non-differentiated tumours (anaplastic carcinoma). Papillary carcinoma is the thyroid cancer known to be caused by ionizing radiation, as shown among the atomic bomb survivors (Wood *et al.*, 1969) and recently in the Chernobyl area. In a study of 577 Ukrainian patients < 19 years of age with a diagnosis of thyroid cancer (Tronko *et al.*, 1999), 290 cases of thyroid carcinomas were evaluated histopathologically and 93% were found to be papillary carcinomas. Similar frequencies were seen in a study of 4296 patients in the USA previously irradiated for benign disorders in the head-and-neck area before the age of 16 years. Forty-one thyroid cancers were found in children who were < 20 years when the cancer developed, and 95% of these were papillary carcinomas (Viswanathan *et al.*, 1994). Thyroid nodules have also been related to exposure to radioiodine (Schneider *et al.*, 1993; Hall *et al.*, 1996a).

2.7.1 *Iatrogenic exposure*

The effects of exposure to radioiodine have been reviewed extensively (UNSCEAR, 1994), and information is also available from several large follow-up studies, the major ones being listed in Table 60. ^{131}I is used for diagnostic and therapeutic purposes (at higher doses).

In reviewing what is known of the carcinogenic effect of medical use of radioiodines in humans, the effects are divided into risks for thyroid cancer, leukaemia and other cancers. Since age at the time of exposure has a strong effect on the risk for radiation-induced cancer, special emphasis is placed on evaluating this modifier of risk.

(*a*) *Thyroid cancer*

Thyroid carcinomas vary in histology, clinical presentation, response to treatment and prognosis. The carcinogenic effect of ^{131}I is less well understood than that of external photon radiation. Before the Chernobyl accident, the effects of radioiodine in children had not been studied to any extent, since children are rarely examined medically or treated. The childhood thyroid gland, red bone marrow and premenopausal female breast are the most radiosensitive organs in the body. Although thyroid carcinomas are known to be more aggressive in children (Viswanathan *et al*., 1994), their prognosis is better than that of adults. Several risk factors have been suggested for thyroid cancers, including a history of benign nodules, miscarriages, iodine deficiency or excess and an elevated level of thyroid-stimulating hormone, but only ionizing radiation has been found to have a causative effect (La Vecchia *et al*., 1999; Negri *et al*., 1999).

Among survivors of the atomic bombings, the most pronounced risk for thyroid cancer was found among those with a dose to the thyroid of > 1 Sv before the age of 10 years, and the highest risk was seen 15–29 years after exposure; the risk subsequently began to decline, but it was still elevated 40 years after exposure (Thompson *et al*., 1994; Ron *et al.*, 1995). In a pooled analyses of seven cohorts of individuals exposed to ionizing radiation, Ron *et al*. (1995) found an ERR at 1 Gy of 7.7 (95% CI, 2.1–28.7) for persons exposed in childhood. They also reported that the ERR decreased by a factor of about 2 for each successive five-year interval of age at exposure over the range 0–14 years of age.

The National Council on Radiation Protection and Measurements (1985) estimated that the RBE of the thyroid dose from ingested or inhaled ^{131}I compared with X-rays was 0.1–1.0, on the basis of experimental studies. The report recommended that 0.3 was the highest credible value for radiation protection purposes. The report also stated that the RBE of ^{131}I relative to X-rays may be lower at high doses and dose rates, and higher (nearer to that of X-rays) at low doses and dose rates. Walinder (1972), in his experiment in mice (see section 4), obtained an RBE of 0.18 with ^{131}I doses to the thyroid in the range 22–160 Gy, whereas Lee *et al.* (1982), in their experiment in rats, found near equivalence after injecting doses giving 0.8, 3.3 and 8.5 Gy to the thyroid. Laird (1987)

Table 60. Major cohorts of patients exposed to radioiodine

Reference	Study	Type of study	Characteristics	Follow-up (years, mean), person–years of observation	Site, number of cancer cases, SIR or SMR (95% CI)
Hall *et al.* (1996b)	Diagnostic (Sweden)	Incidence	34 104; 80% women; age, 1–75	5–39 (24), 653 093	Thyroid: 67, 1.35 (1.05–1.71) diagnosed > 5 years after exposure
Hall *et al.* (1992a); Holm *et al.* (1991)	Hyperthyroid patients (Sweden)	Incidence/ mortality	10 552; 82% women; age, 13–74	1–33 (15), 139 018	*Incidence (Holm* et al.*, 1991)* Stomach: 92, 1.05 (0.85–1.28) Kidney: 66, 1.39 (1.07–1.76) Brain: 48, 1.30 (0.96–1.72) Thyroid: 18, 1.29 (0.76–2.03) *Mortality (Hall* et al.*, 1992a)* Stomach: 54, 1.41 (1.06–1.85) Kidney: 15, 0.90 (0.51–1.49) Thyroid: 12, 1.95 (1.01–3.41)
Ron *et al.* (1998)	Hyperthyroid patients (USA)	Mortality	20 949 iodine-exposed; 8054 only iodine-exposed; 10 874 unexposed; 79% women; age, < 80	1–44 (21), 385 468 (iodine-exposed) 141 543 (only iodine-exposed)	*Iodine-exposed* Thyroid: 24, 3.94 (2.52–5.86) Lung: 295, 1.06 (NG) Breast: 248, 1.10 (NG) *Only iodine-exposed* Thyroid: 11, 4.91 (2.45–3.41)
Franklyn *et al.* (1999)	Hyperthyroid patients (United Kingdom)	Incidence/ mortality	7417; 83% women; age, 49–≥ 70	1–≥ 20, 72 073	Thyroid: Incidence: 9, 3.25 (1.69–6.25) Mortality: 5, 2.78 (1.16–6.67) Small bowel: Incidence: 6, 4.81 (2.16–10.7) Mortality: 6, 7.03 (3.16–15.7)

Table 60 (contd)

Reference	Study	Type of study	Characteristics of the cohort	Follow-up (years, mean), person–years of observation	Site, number of cancer cases, SIR or SMR (95% CI)
Hall *et al.* (1991)	Thyroid cancer patients (Sweden)	Incidence	834 exposed[a], 1121 unexposed; 75% women; age, 5–75	2–34 (14), 10 073 in the ^{131}I treated group; 15 757 in the untreated group	Exposed: Salivary glands: 3, 15.0 (3.09–43.8) Kidney: 7, 3.00 (1.21–6.19) Unexposed: Salivary glands: 0, 0 (0.00–12.7) Kidney: 5, 1.48 (0.48–3.45)
de Vathaire *et al*. (1997)	Thyroid cancer patients (France)	Incidence	1771 patients: 846 received ^{131}I for therapy, 651 received ^{131}I for diagnosis; 274 unexposed; 79% women; age, 5–89	2–37 (10), 14 615	Colorectal, 1771 patients 0–0.19 GBq[b]: 6, 1.0 (reference category) > 0.19–3.7 GBq: 1, 1.4 (0.2–6.8)[c] > 3.7–7.5 GBq: 4, 4.0 (1.3–12.2) [c] > 7.5 GBq: 2, 4.9 (1.2–18.5) [c]

SIR, standardized incidence ratio; SMR, standardized mortality ratio; CI, confidence interval

[a] Individual doses based on iodine administered, 24-h uptake

[b] Cumulative activity of ^{131}I (GBq) [10^9 Bq] administered 5 years or more before diagnosis of colorectal cancer

[c] 90% CI

conducted parallel and combined analyses of six cohorts of children exposed to external radiation or ^{131}I and one cohort of adult survivors of the atomic bombings, and re-evaluated data from the large experimental study of Lee *et al*. (1982) that was specifically designed to investigate the RBE of ^{131}I. By combining the evidence from the epidemiological and experimental studies, Laird (1987) estimated a risk ratio of 0.66 (95% CI, 0.14–3.15). The RBE value at low doses remains a contentious issue (see section 4).

A Swedish study of 34 104 patients who had received ^{131}I for diagnostic purposes, whose doses were quantified on the basis of the administered dose of iodine and 24-h uptake, did not show an increased risk for thyroid cancer (Hall *et al*., 1996b; see Table 60). The size of the gland was known for half of the patients, but addition of this information did not alter the results. It should be emphasized that only 7% (n = 2408) of the patients were < 20 years of age at time of exposure and that three cases of thyroid cancer were found in this group, giving a non-significant SIR of 1.69 (95% CI, 0.35–4.93) with a mean dose of 1.5 Gy to the thyroid.

Several studies of the carcinogenic effect of radioiodine involved patients treated for hyperthyroidism, of whom nearly all were adults (Holm *et al.*, 1991; Hall *et al*., 1992a, 1993; Ron *et al*., 1998; Franklyn *et al*., 1999; see Table 60). In the two most recent studies, elevated risks were found for death from thyroid cancer (Ron *et al*., 1998; Franklyn *et al.*, 1999) and for the incidence of this cancer (Franklyn *et al*., 1999) after treatment of adults with ^{131}I for hyperthyroidism; this result contrasts with those of previous studies of hyperthyroid patients (Holm *et al.*, 1991; Hall *et al*., 1992a, 1993) and of patients examined with ^{131}I (Hall *et al*., 1996b). The reason for referral, i.e. the underlying thyroid disorder, could have influenced the risk, since the highest risk was seen < 5 years after exposure. The risk was seen primarily among patients with toxic nodular goitre, which has been identified as a risk factor for thyroid cancer; and the authors of the study in the USA suggested that some of the patients might have had an undiagnosed thyroid cancer at the time of treatment with ^{131}I (Ron *et al.*, 1998). In the British study (Franklyn *et al*., 1999), no dose–response relationship was found, again indicating that the underlying disease could have influenced the results.

The dose to the thyroid (60–100 Gy) received by most hyperthyroid patients has been considered to induce cell killing rather than a carcinogenic effect (Hall *et al.*, 1992a), but the dose to abnormal thyroid glands is difficult to measure. Non-uniform distribution of radioiodine and, thus, of the dose delivered, results in very high doses to some parts, while other areas are probably exposed to comparatively low doses.

At present, there is no direct evidence that medical use of ^{131}I induces thyroid cancers in humans, regardless of the reason for exposure. This result is not surprising, however, because few children were studied. There is also little evidence that the risk is increased by exposure of adults to γ-radiation or X-rays. For example, in the studies of atomic bomb survivors, no evidence was found of an increased risk for individuals exposed after the age of 20 (Thompson *et al*., 1994).

(*b*) *Leukaemia*

The incidence of leukaemia was studied in 46 988 persons (80% males) exposed to ^{131}I for diagnostic purposes (dose to the bone marrow, 0.01–4.44 mGy) or for treatment of hyperthyroidism (1–810 mGy) or thyroid cancer (22–2226 mGy). A total of 130 leukaemias was found, excluding chronic lymphocytic leukaemia (SIR, 1.09; 95% CI, 0.91–1.29), and the mean absorbed dose to the bone marrow was 14 mGy, which might partly explain the absence of an increased risk or, more correctly, the lack of statistical power in the study (Hall *et al*., 1992b). Ron *et al*. (1998) studied the risk for leukaemia other than chronic lymphocytic leukaemia in patients treated for hyperthyroidism after a mean absorbed bone-marrow dose of 42 mGy and found a SMR of 1.22 (not significant; 53 cases) with ^{131}I treatment in any combination with thyroid surgery or antithyroid drugs, and a SMR of 1.12 (not significant; 18 cases) for persons treated with ^{131}I only. By comparison, no excess risk for leukaemia was seen among about 23 300 atomic bomb survivors who received doses to the bone marrow of 0.01–0.99 Gy [mean, 38 mGy] (Preston *et al*., 1994).

Edmonds and Smith (1986) found three cases of leukaemia, with 0.25 expected ($p = 0.02$); Hall *et al.* (1991) found four cases of leukaemia, with 1.6 expected (SIR, 2.44; 95% CI, 0.66–6.25) and Brincker *et al.* (1973) found two cases, with 0.097 expected ($p < 0.05$), in thyroid cancer patients treated with relatively high doses of ^{131}I. Nevertheless, the available data on patients exposed to low-LET radiation do not on balance indicate an increased risk associated with radioiodine, even though the precision of these studies was low, owing to the low absorbed doses to the bone marrow.

(*c*) *Cancers at other sites*

The only tissues that receive doses of radioiodine that could have a measurable carcinogenic effect, other than thyroid and bone marrow, are the gastrointestinal and urinary tracts. Breast cancer is also discussed, since an increased risk has been found in patients treated for thyroid cancer or hyperthyroidism.

(i) *Gastrointestinal tract*

In a study of 10 552 patients treated with ^{131}I for hyperthyroidism, an increased rate of death from stomach cancer was seen when compared with national rates (SMR, 1.41; 95% CI, 1.06–1.85) (Hall *et al*., 1992a). A non-significant increasing risk with increasing dose of iodine administered was seen. Individual doses were not available. It is possible that the underlying disorder, e.g. Graves disease, is associated with atrophic gastritis, which in turn is related to gastric cancer.

Franklyn *et al*. (1999) studied 72 073 person–years of follow-up after ^{131}I treatment for hyperthyroidism and found significantly increased incidence and mortality rates for cancer of the small bowel (SIR, 4.81; 95% CI, 2.16–10.7; six observed cancers; SMR, 7.03; 95% CI, 3.16–15.7; six fatal cancers). de Vathaire *et al*. (1997) studied 1771 patients who had been treated for thyroid cancer, of whom 846 had received ^{131}I for therapy, 651 had received ^{131}I for diagnosis and 274 had not received ^{131}I. The mean

cumulative activity administered was 7.2 GBq for therapy and 0.6 GBq for diagnosis. Eighty patients developed a second solid malignancy, of which 13 were colorectal cancers, and the risk for this cancer in 11 cases was significantly related to the cumulative dose of ^{131}I administered ≥ 5 years previously (ERR, 0.5/GBq; $p = 0.02$).

Increased risks for cancers of the gastrointestinal tract are probably difficult to identify since the doses received are low, e.g. the dose to the colon is approximately 50 mGy (Hall *et al*., 1992a).

(ii) *Urinary tract*

The urinary bladder concentrates iodine, and the dose of radioiodine to the bladder wall is highly dependent on the uptake of radioiodine by the thyroid (Smith & Edmonds, 1984; Edmonds & Smith, 1986): the higher the thyroid uptake, the lower the urinary bladder dose, since radioiodine is incorporated into thyroid hormones. At the low uptakes in thyroid cancer patients, the dose to the urinary bladder has been estimated to be 2 Gy (Hall *et al*., 1991). In one study, the incidence of and mortality from urinary bladder cancer were increased among thyroid cancer patients treated with ^{131}I (Edmonds & Smith, 1986), but this result contrasted with the findings of others (Hall *et al*., 1991; de Vathaire *et al*., 1997). The dose to the urinary bladder in patients treated with radioiodine for hyperthyroidism is probably one-tenth of that received by thyroid cancer patients (Ron *et al.*, 1998), and no increase in risk has been found in hyperthyroid patients treated with ^{131}I (Hall *et al*., 1992a; Ron *et al*., 1998; Franklyn *et al*., 1999).

(iii) *Breast*

In a study in the USA, a nonsignificantly increased risk for breast cancer was seen among hyperthyroid patients receiving ^{131}I when compared with those treated by other means (standardized rate ratio [SRR], 1.9; 95% CI, 0.9–4.1) (Goldman *et al*., 1988), but no relation with dose was seen. When this cohort was included in a larger study, no significant excess of breast cancer was observed (SMR, 1.10; Ron *et al*., 1998). In a Swedish study of hyperthyroid patients treated with ^{131}I, the mean absorbed dose to the breast was 50 mGy; no increased risk was noted (SMR, 0.86; Hall *et al*., 1992a).

2.7.2 *Accidents in or discharges from nuclear facilities*

During accidents at nuclear installations, radioiodines and other radionuclides may be released into the environment. Table 61 summarizes the main accidents and releases from nuclear facilities and shows the amount of activity released, the populations exposed and the dose distributions.

The releases from the accident at the Three Mile Island reactor in Pennsylvania, USA, in 1979 were relatively small and were largely minimized by the containment building. The releases from the fire at the Windscale reactor in the United Kingdom in 1957 and particularly those from the Hanford site in Washington State, USA, over the period 1944–47 were larger and covered a wider geographical area. The releases

Table 61. Characteristics of the main large-scale accidental or non-routine releases of ^{131}I

Location (reference)	Cause	Approximate quantity released	Date	Number of exposed persons	Estimated doses
Hanford, WA, USA (UNSCEAR, 2000)	Release of radioactive iodine	^{131}I: 20–25 × 10^{15} Bq [PBq] into the atmosphere	1944–57	270 000 3193 children born in 7 counties between 1940 and 1946	Thyroid: 95%, < 0.3 Gy range, 0–2.84 Gy median, 0.1 Gy mean, 0.186 Gy
Windscale, United Kingdom (UNSCEAR, 1993; Cardis, 1996)	Fire in reactor	^{131}I: 7 × 10^{14} Bq (over South Lancashire and Yorkshire)	1957	Not reported	Thyroid: 100–2500 μSv Children, 100 mGy Adults, 10 mGy
Three Mile Island, PA, USA (UNSCEAR, 1993)	Human error in power reactor	^{131}I: 550 × 10^{9} Bq [GBq] into the atmosphere	1979	Population within 80 km	External γ-radiation average, 15 μSv maximum, 850 μSv
Chernobyl, Ukraine (Ilyin *et al.*, 1990; UNSCEAR, 2000)	Destruction of reactor core	^{137}Cs: 85 × 10^{15} Bq ^{131}I: 1760 × 10^{15} Bq	1986	135 000 evacuees from 30-km zone (new estimate, 116 000); 270 000 in strict control zones	Whole-body γ-radiation: range, 30–≥ 500 mSv average, 120 mSv Thyroid, ^{131}I, children average, 0.3 Gy range, 0.1–> 2.5 Gy Committed effective dose equivalent from γ-radiation: average, 60 mSv 4%, > 100 mSv 800 persons, > 200 mSv Thyroid, ^{131}I, children range, 0.1–>10 Gy

from the Chernobyl reactor accident in the Ukraine in 1986, however, were much more extensive, and dispersed radionuclides were measured in northern Europe (UNSCEAR, 1988). Apart from persons in the area surrounding the reactor, however, almost all individuals received whole-body doses that were a small fraction of the annual dose from natural background radiation.

(*a*) *Windscale, United Kingdom*

The fire at the Windscale works of the Atomic Energy Authority at Sellafield in October 1957 (see section 1.1.2(*c*)(i)) resulted in the release of an unknown quantity of ^{131}I into the environment. Approximately 8×10^{14} Bq [800 TBq] of ^{131}I present in a cloud of radioactive material passed over south Lancashire and Yorkshire (Crabtree, 1995). Maximum depositions of ^{131}I were found in the Seascale-Drigg area, 3–6 km from Windscale (Chamberlain & Dunster, 1958). The doses to the thyroid were estimated to be small: < 0.67 μSv/year of ^{129}I on the basis of analyses at autopsy and a similar dose from ^{131}I. The rates of registration of thyroid cancer in Cumbria during 1969–86 were positively correlated with decreasing distance from Sellafield (Bowlt & Tiplady, 1989).

(*b*) *Hanford, Washington, USA*

At the Hanford nuclear weapons site in the USA, major releases of ^{131}I into the atmosphere were made between 1944 and 1957. The total activity released is estimated to have been of the order of $20–25 \times 10^{15}$ Bq (UNSCEAR, 2000), while 18×10^{15} Bq were released between 1944 and 1946 (UNSCEAR, 1993). Individual doses to the thyroid were reconstructed for 3193 persons who had been exposed as children at the time of these releases, by the fact of having been born in one of seven counties of Washington State between 1940 and 1946. The mean and median doses were estimated to have been 186 mGy and 100 mGy respectively, with a skewed distribution (range, 0–2840 mGy) (UNSCEAR, 2000). The preliminary results of an epidemiological study of thyroid cancer in this population have been published (UNSCEAR, 2000): no association was observed between thyroid cancer risk and estimated thyroid dose. [The Working Group recognized the difficulties of reconstructing doses after several decades on the basis of dietary recall and past information on radionuclide releases.]

(*c*) *Three Mile Island, Pennsylvania, USA*

During the accident at Three Mile Island in 1979 (see section 1.1.2(*c*)(ii)), 550×10^9 Bq of ^{131}I were released into the environment (UNSCEAR, 1993). Surveillance of the mortality rates among 32 135 persons who were living near the plant on the date of the accident does not provide consistent evidence that the radioactivity released during the accident had a significant effect (Talbott *et al.*, 2000).

(*d*) *Chernobyl, Ukraine*

This section describes the Chernobyl accident and specific investigations on cancers occurring in the populations in surrounding areas. The effects of external exposure of the 600 000–800 000 'clean-up' workers (UNSCEAR, 2000) and of the general population are summarized in the first monograph on ionizing radiation (IARC, 2000). See also section 1.1.2(*a*).

The accident at the Chernobyl reactor occurred on 26 April 1986 during an experimental test of the electrical control system while the reactor was shut down for routine maintenance. A sudden power surge caused a steam explosion that ruptured the reactor vessel. An intense graphite fire burned for 10 days, and large amounts of radioactive materials were released. As discussed in section 1, the main radionuclides released from the reactor to which persons were exposed internally were ^{131}I, ^{134}Cs and ^{137}Cs. ^{131}I has a short radioactive half-life (eight days) but can be absorbed relatively rapidly from air, milk and leafy vegetables. It is then localized in the thyroid gland. Because of the dietary patterns of infants and children, the size of their thyroid glands and their metabolism, they usually receive higher doses of radiation than adults. However, the doses received are difficult to estimate unless the concentrations of ^{131}I in foods or in the thyroid gland were measured within days of the accident (UNSCEAR, 2000).

The isotopes of caesium have relatively longer half-lives (^{134}Cs, two years; ^{137}Cs, 30 years), and exposure after ingestion or from their deposition on the ground is usually longer.

The Chernobyl accident resulted in widespread radioactive contamination of areas of Belarus, the Russian Federation and the Ukraine, which were inhabited by several million people. Currently, about 7 million people live permanently in areas where the ^{137}Cs deposition density is > 37 kBq/m^2, covering about 131 000 km^2 (Balonov *et al.*, 1996; Cardis *et al.*, 1996; revised to 146 000 km^2 by UNSCEAR, 2000). The doses received by these persons resulted from external exposure to the passing cloud, from radionuclides deposited on the ground and other surfaces and from internal exposure by inhalation of material from the passing cloud in the first days and ingestion of radionuclides in foods subsequently. The estimated collective doses in various population groups are shown in Table 62. The average whole-body doses of the general population living in contaminated areas were 10–60 mSv.

Much larger doses to the thyroid (up to several Gy) were received by persons (particularly children) living in the most heavily contaminated regions in the first few days after the accident. Although the thyroid was exposed both externally and internally, most of the dose in contaminated regions was from isotopes of iodine (UNSCEAR, 2000).

Persons who participated in the clean-up of the Chernobyl accident, the so-called 'liquidators', may have received substantial doses of radiation. As shown in Table 62, the average dose of those who worked in 1986–87 was 100 mSv, mainly from external radiation. Studies of the cancer risk of Chernobyl liquidators are therefore not

Table 62. Estimates of collective equivalent doses of populations in contaminated areas of Belarus, Russian Federation and the Ukraine after the Chernobyl accident

Population	Average dose received (mSv)	Effective number	Collective dose (person–Sv)
Evacuees	11–17	135 000	1600
Liquidators (1986–87)	100	200 000	20 000
Persons living in contaminated areas[a]:			
Deposition density of ^{137}Cs > 555 kBq/m^2	50–60	270 000	10 000–20 000
Deposition density of ^{137}Cs 37–555 kBq/m^2	6–20	6 800 000	35 000–100 000

From Cardis *et al.* (1996)

[a] Doses for 1986–95; over 1996–2056, the collective dose will increase by approximately 50%.

reviewed here, except for those on thyroid cancer, as substantial doses to the thyroid from iodine isotopes may have been received by some of the liquidators who arrived on the site shortly after the accident. As discussed in section 1, the doses of populations exposed outside the European part of the former USSR were also mainly from external radiation. Therefore, this section is restricted to studies conducted in Belarus, the Russian Federation and the Ukraine.

Although a number of studies have addressed the association between exposure from radionuclides released in the Chernobyl accident and late health effects, it is still too early to evaluate the risks for most types of cancer, as only 14 years have passed. Moreover, the level of adequacy of the dosimetric data for external and internal exposures is still questionable. Most of the publications to date have focused on the increased incidences of thyroid cancer and leukaemia, sites for which the latency is shorter than those for cancers at other sites.

(i) *Thyroid cancer in young people*

Most of the studies completed to date are of the descriptive type, in which average population exposures are correlated with average rates of cancer incidence during specific periods. When no individual dosimetry is performed, it is difficult to evaluate whether the effects are radiation-related, and it is impossible to make reliable quanttative estimates. Reconstruction of individual doses is a key element of future research on radiation-associated cancers related to the Chernobyl accident (UNSCEAR, 2000).

A significant increase in the incidence of thyroid cancer in childhood has been observed in Belarus and, later, in the Russian Federation and the Ukraine since 1990. Table 63 (Stsjazhko *et al*., 1995) illustrates the time trends in the incidence of thyroid cancer in the three countries up to the end of 1994. Although reports of such increases were initially met with scepticism, there is now strong circumstantial evidence that these increases are related to the release of iodine isotopes during the Chernobyl

Table 63. Distribution of cases of thyroid cancer in children under the age of 15 years at diagnosis, in Belarus, the Russian Federation and the Ukraine

Location	1981–85		1986–90		1991–94	
	No.	Rate/10^6	No.	Rate/10^6	No.	Rate/10^6
Belarus (whole country)	3	0.3	47	4.0	286	30.6
Gomel	1	0.5	21	10.5	143	96.4
Russian Federation						
Bryansk and Kaluga regions[a]	0	0	3	1.2	20	10.0
Ukraine (whole country)	25	0.5	60	1.1	149	3.4
Five most northerly regions	1	0.1	21	2.0	97	11.5

From Stsjazhko *et al*. (1995)

[a] No data were available for the Russian Federation as a whole

accident. A total of 1420 thyroid tumours were diagnosed during 1990–97 among persons who were < 18 years of age at the time of exposure (UNSCEAR, 2000). Most of the tumours have been reviewed by international groups of pathologists and endocrinologists, with over 90% agreement (Williams, 1996). Nearly all the tumours were papillary thyroid carcinoma (solid and papillary forms), and histological studies have identified a subtype of papillary carcinoma — with a solid/follicular architecture — that is fairly prevalent in children from contaminated areas; this subtype is rarely found in adults (Williams *et al*., 1996).

Most of the tumours have been observed among subjects who were very young at the time of the accident: in Belarus, over half of the tumours occurred in people who were < 6 years old at the time of the accident (Demidchik *et al*., 1999). In a series of 472 children with thyroid cancer diagnosed up to 1995 in Belarus, only two had been conceived after the accident; nine had been exposed *in utero*, and 88% were under the age of 15 at the time of diagnosis (Pacini *et al*., 1997). In the Ukraine, over 60% of the children in whom thyroid cancer was diagnosed at the end of 1997 were under 15 years of age at the time of diagnosis (Tronko *et al*., 1999).

Like childhood tumours elsewhere, most of the tumours in children in contaminated areas had aggressive characteristics. In Belarus and the Ukraine, the tumours were generally > 10 mm in diameter and showed extrathyroidal growth (48–61% of cases), lymph node metastases (59–74%) and distant (mainly lung) metastases (7–24%) (Abelin *et al*., 1994; Nikiforov & Gnepp, 1994; UNSCEAR, 2000). Nevertheless, the prognosis of these tumours is good, and fewer than five deaths have been reported.

A number of ecological studies of thyroid cancer incidence in young people in relation to estimated dose at the settlement level have been carried out in the Ukraine (Sobolev *et al*., 1996; Goulko *et al*., 1998; Jacob *et al*., 1998), Belarus (Kenigsberg *et al*., 1996; Bleuer *et al*., 1997; Heidenreich *et al*., 1999), the Russian Federation (Parshkov *et al*., 1997) and across Belarus and the Russian Federation (Jacob *et al*.,

1999). These studies show a good correlation between the estimated dose and thyroid cancer incidence; however, because of uncertainties in estimating the dose to the thyroid and the incomplete case ascertainment in some areas and age ranges, risk estimates derived from such studies must be interpreted with caution.

A case–control study designed to test the hypothesis that the Chernobyl accident resulted in an increased incidence of thyroid cancer was carried out by Astakhova *et al*. (1998) in Belarus. The study population comprised 107 confirmed cases of thyroid carcinoma (105 papillary, two follicular) diagnosed or treated between 1987 and mid-1992 at the Aksakovtchina Clinic (a national referral centre) or the National Thyroid Surgery Centre at the Minsk State Medical Institute, where all cases of childhood (< 15 years) thyroid cancer in Belarus were seen at that time. The individual doses to the thyroid were inferred from the mean dose of adults in the settlement and the deposition density of ^{131}I or ^{137}Cs in settlements where doses to the thyroid had been 'measured'. Information on milk consumption and prophylactic intake of stable iodine was not taken into account. The contributions to the dose from external radiation, short-lived radioisotopes of iodine and other long-lived radionuclides were judged to be small in comparison with the dose from ^{131}I and were not considered. Because of uncertainties about individual doses, they were grouped into three categories, < 0.3, 0.3–0.9 and ≥ 1 Gy. Two sets of controls were matched to each case. Type I controls (107) were drawn at random from the general population of children in the 'exposure zone', matched on age, sex and urban or rural area of residence in 1986. They were chosen at random from the individual medical records of the polyclinics in each district in proportion to that district's 1986 population. Type II controls (107) were selected from among children who had had the same opportunity for diagnosis as the cases: that is, cases diagnosed in the framework of a systematic endocrinological screening programme were matched to controls who had participated in the screening. They were matched on age and sex but not on geographical location. A strong association was found between dose category and risk for thyroid cancer, with or without adjustment for age, sex, year of diagnosis, ^{131}I in soil and mode of diagnosis. The highest odd ratios were seen for children in rural areas of the Gomel region: 10.42 (95% CI, 3.46–31.25) with type I controls and 7.41 (2.5–21.7) with type II controls, for exposure to ≥ 0.3 Gy versus < 0.3 Gy. Fifteen of the 17 patients and three of the four controls who had been exposed to doses ≥ 1 Gy originated from the rural Gomel region. [The Working Group noted that the male:female ratio is close to 1, suggesting a possible screening effect, and also noted the uncertainty of the dose estimates.]

Overall, the number of thyroid cancers found among persons exposed in childhood, particularly in the severely contaminated areas of the three affected countries, is considerably greater than that expected on the basis of previous knowledge. Such a high incidence and short induction period have not been experienced in other exposed populations, and other factors have almost certainly affected the reported increase. These include screening bias, iodine deficiency and supplementation, both at the time of the accident and in following years, a possible genetic predisposition and the role of short-

lived isotopes of iodine (Cardis *et al.*, 1996; Astakhova *et al.*, 1998; Cardis *et al.*, 1999). If the current trend continues, more thyroid cancers can be expected to occur, especially among people exposed at young ages. The most recent findings indicate that the risk for thyroid cancer among people who were < 4–5 years old at the time of the accident is continuing to increase (UNSCEAR, 2000). [The Working Group noted that the time trends in age-specific incidence for people exposed at later ages are somewhat erratic and are difficult to interpret, as the treatment of adolescent and adult cases is much less centralized than that of childhood cases.]

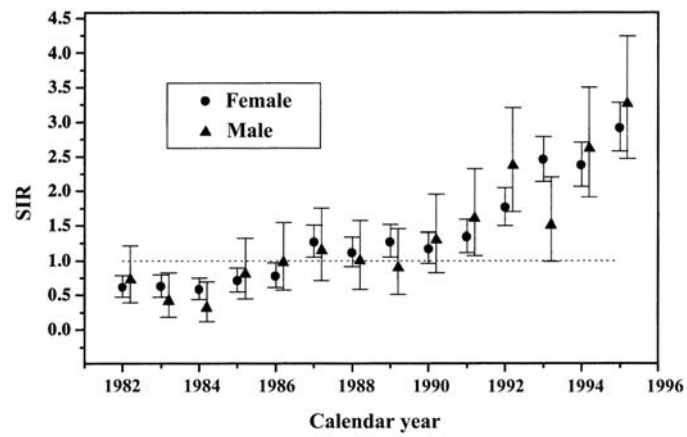
At present, it is difficult to quantify the risk of radiation-induced thyroid cancer for exposed children because (1) intense screening for thyroid cancer played some role in the detection of thyroid cancers; (2) iodine deficiency and the associated mild goitre could have contributed to the increased risk; (3) assessment of individual exposure is complex and depends on reconstructing the dietary habits of children many years in the past and estimating the radioactive iodine contents of various foods; and (4) the contribution to dose of radionuclides of iodine other than ^{131}I is not well defined, whereas these radionuclides have shorter half-lives and greater β-particle emission energies, exposing the thyroid gland more uniformly than ^{131}I and at a higher dose rate. Nevertheless, the more than 1000 thyroid cancers that have been detected among persons exposed as children are one of the clear consequences of the Chernobyl accident.

(ii) *Thyroid cancer in adults*

The incidence of thyroid cancer in the general population of children and adults in the contaminated territories of Belarus, the Russian Federation and the Ukraine and among the 'liquidators' who participated in the clean-up of the Chernobyl accident both in the 30-km area around the reactor and in contaminated regions of Belarus and the Ukraine has also been studied.

Ivanov *et al*. (1999a,b) analysed the trends in thyroid cancer incidence among persons aged 0–60 years in the four most heavily contaminated regions of the Russian Federation (Bryansk, Kaluga, Orel and Tula). The total population of these regions was 4.33 million people, and the number of children and adolescents was 1.217 million. Cases of thyroid cancer were identified from the regional oncological dispensary in each region, and 3082 cases were detected between 1982 and 1996. Of these, 2618 were among women (50 cases among girls aged 0–17), and 464 were among men (28 cases among boys aged 0–17). There were 178 cases among persons who were children or adolescents at the time of the Chernobyl accident (46 boys and 132 girls). The time trends in SIRs for thyroid cancer are shown in Figure 9 for the study regions and for the whole territory of the Russian Federation. During the period 1982–86, the SIRs in these regions were lower than those for the country as a whole. The SIR increased immediately after the accident and remained approximately constant over the period 1987–91, after which it increased substantially with time. The authors attributed the immediate increase (1987–91) to a screening effect, with the introduction of a special examination system in these regions, and the later increase to an effect of radiation from

Figure 9. Trends in the standardized incidence ratio (SIR) for thyroid cancer in Bryansk, Kaluga, Orel and Tula as compared with that in the Russian Federation as a whole



From Ivanov *et al.* (1999b). Bars are 95% confidence intervals.

the accident. [The Working Group noted that studies of external exposure indicate that the risk for radiation-induced thyroid cancer is expected to be low in persons exposed as adults.]

Ivanov *et al*. (1997a) investigated the incidence of thyroid cancer among 'liquidators' who had worked to clean up the Chernobyl catastrophe. The cohort consisted of 167 862 persons, all of whom were registered in the Russian National Medical Dosimetric Registry. A total of 43 cases of thyroid cancer were found between 1986 and 1994 among the 136 367 liquidators who had worked at Chernobyl during 1986–87. Their average age at the time they entered the 30-km area of the Chernobyl nuclear power plant was 33 years, and their mean external whole-body dose was 0.14 Gy. The expected number of thyroid cancers was 9.44. The SIR for the latent period (1986–90) was 2.6 (95% CI, 1.34–4.52) and that for the post-latent period (1991–94) was 6.45 (95% CI, 4.38–9.15); four more thyroid cancers were detected in the liquidators who worked in 1988–90. The authors found that screening had affected the detection of thyroid cancer during the first years after the accident.

Cardis *et al*. (1996) analysed the cancer incidence of liquidators who had worked in the 30-km zone around the Chernobyl plant in 1986 or 1987 and of the population living in contaminated areas of Belarus, the Russian Federation and the Ukraine. An increased incidence was seen among liquidators in all three countries, although there were relatively few cases (28 cases in 1993–94). The liquidators who worked in the 30-km zone in the first days after the accident may have received significant doses of radiation to the thyroid from short-lived iodine isotopes. The authors noted, however,

that the results must be interpreted with caution, as the liquidators are followed-up much more actively than the general population in the three countries, and, for thyroid cancer in adults, the extent of screening may influence the observed incidence. A 1.5–2-fold increase in the incidence of thyroid cancer was also seen in the general population of the contaminated regions of the three countries. Again, because of heightened awareness of the consequences of the accident and the more intensive medical follow-up of populations living in contaminated regions, these findings must be interpreted with caution, and further analyses are needed before the finding can be confirmed or refuted. This is particularly important, as no excess of thyroid cancer has been found among persons exposed when over the age of 20 in studies of populations exposed to external radiation (Thompson *et al.*, 1994) or to medical treatment with ^{131}I (see section 2.7.1).

(iii) *Other cancers*

Prisyazhniuk *et al*. (1991, 1995, 1996) analysed trends in cancer incidence in the Ukraine and in the contaminated regions of Belarus, the Russian Federation and the Ukraine. Although they observed increased incidences of all cancers and of leukaemia, they noted that the increases were consistent with pre-existing trends in the incidence of these diseases. The increases were, moreover, not related to the levels of exposure in the regions. The predominant difference from rates before the Chernobyl accident was in the rate of cancers among people in the oldest age group considered (65 years and over). The rate began to increase as early as one year after the accident, and therefore probably reflected better ascertainment of disease in this population. The increase in the incidence of leukaemia was accounted for primarily by chronic lymphocytic leukaemia, a subtype that has not been associated with exposure to radiation in other studies.

Cardis *et al*. (1996) found no increase in the incidence of all cancers in populations of contaminated regions of the Ukraine. In Belarus and the Russian Federation, a marginally statistically significant 3% increase in deaths from any cancer was noted, while no increase was observed in the incidence of leukaemia in any of the three countries. Although several authors have reported an increased incidence of leukaemia among subgroups of liquidators, these increases are not consistent. Thus, 46 cases were reported among the liquidators in the three countries during 1986–87; a non-significant twofold increase (based on nine observed cases) was observed in Belarus; in the Russian Federation, no significant difference in leukaemia incidence was found between liquidators and the general population; and in the Ukraine, a significant increase in the incidence of leukaemia was reported. Because of the more intensive medical follow-up of the populations living in contaminated regions, these findings must be interpreted with caution, and further analyses are needed before they can be confirmed or refuted.

Ivanov *et al*. (1997b) studied the cancer risk in Kaluga oblast of the Russian Federation 10 years after the Chernobyl accident in order to assess the effect of radiation on the existing rates of cancer incidence and mortality. Time trends and relative population risks were analysed. The only statistically significant effect of

radiation on cancer incidence was on thyroid cancer in women. The rates of cancer incidence and mortality in the contaminated areas generally reflected the changes in cancer incidence in the region as a whole.

In 1986, a special registry of 'haemoblastoses' was set up in the most heavily contaminated areas (^{137}Cs contamination, ≥ 550 GBq/km^2) of Bryansk region in the Russian Federation. Information on 2832 cases of haemoblastosis was accumulated in the registry up to the end of 1992. No significant difference was seen in the annual average incidence rate of specific haemoblastoses between areas with different degrees of contamination (Osechinksy *et al*., 1994).

Ivanov *et al*. (1998) analysed the incidence of leukaemia among infants in Belarus after the Chernobyl accident and compared the data with those from Germany and Greece, where increased incidences were reported in children who were *in utero* at the time of the accident. As the contamination in Belarus was far heavier than that in the other countries, it might be expected that any excess of infantile leukaemia due to prenatal exposure would continue beyond the first year after the accident. In the most heavily contaminated areas of Gomel and Mogiljev, the rate ratio for infant leukaemia incidence was increased (1.51; 95% CI, 0.63–3.61), but not significantly. Comparison of the incidence rates in Belarus, Germany and Greece in relation to the average ^{137}Cs contamination in those countries (> 60 kBq/m^2 [> 60 GBq/km^2] in Belarus and < 6 kBq/m^2 [< 6 GBq/km^2] in both Germany and Greece) led the authors to conclude that a causal relationship between the reported increases and the Chernobyl accident was difficult to accept.

2.8 Phosphorus

Use of radioactive phosphorus in the form of $^{32}PO_4$ for the treatment of polycythaemia vera was introduced in 1939 (Lawrence, 1955; Lawrence *et al.*, 1969). The incidence of this disease is two to three cases per 100 000 per year and is higher in men than in women (Berglund & Zettervall, 1992). ^{32}P has a physical half-life of 14.3 days and emits β-particles. The activities of $^{32}PO_4$ used orally or intravenously are 185–300 MBq (5–8 mCi). After parenteral administration, the skeletal uptake exceeds that of muscle, fat or skin by factors of 4–6 on the first day and 6–10 on the second. After intravenous injection to humans, 5–10% of an administered dose is excreted in the urine within the first 24 h and 20–50% within a week. Less than 2% is excreted in the faeces (Silberstein, 1993).

Few precise data on the dosimetry of phosphorus in humans are available. Spiers *et al*. (1976) measured the dose absorbed by the bone marrow in biopsy samples taken from the iliac crest and the sternum. The biological half-life of ^{32}P in the body was 39 days. The dose absorbed by the marrow in trabecular bone was 24 rad/mCi injected [0.24 Gy per 37 MBq (6.5 nGy/Bq)], and the doses from activity in trabecular bone, marrow and cortical bone were 10, 13 and 1 rad [0.1, 0.13 and 0.01 Gy], respectively. Using a compartmental approach, Seltzer *et al*. (1964) and Mays (1973) found an

average skeletal dose of 300 rad/20 mCi [0.15 Gy/37 MBq (4 nGy/Bq)] administered. ICRP (1993b) published comparable results.

2.8.1 *Haematological malignancies* (see Table 64)

It is now established that polycythaemia vera is a clonal malignancy of the pluripotent haematological stem cell (Adamson *et al.*, 1976; Berk *et al.*, 1986). An increased risk for leukaemia may therefore be a consequence of the natural course of polycythaemia vera. Alternatively, patients with this disease may be more sensitive to the leukaemogenic effects of irradiation than the general population.

As patients with polycythaemia vera must be treated as quickly as possible, it is difficult to obtain precise information on the natural course of the disease. One source of relevant information is Videbaek (1950), who presented data on 125 patients who had been followed-up in several Danish hospitals between 1920 and 1950. These patients were treated by varied protocols, most frequently with phlebotomy and X-rays, but none had been treated with ^{32}P. The median length of survival was 4–5 years for men and 8–9 years for women. The complications were haemorrhage, thrombosis and gastroduodenal ulcer. Eight patients developed fatal malignant tumours; one died from chronic myeloid leukaemia and another from stem-cell leukaemia. The treatment received by the 10 patients who died from a malignancy was not known; however, this study is useful in providing an upper limit to the risk for leukaemia in the natural course of polycythaemia vera.

A second source of information on the risk for leukaemia in the natural course of polycythaemia vera is the report of a subgroup who received no X-rays or ^{32}P in the series assembled by Modan and Lilienfeld (1965). Less than 1% of these patients developed acute leukaemia during 8–25 years of follow-up.

A third source of information on cancer risk in patients with polycythaemia vera in the absence of radiotherapy comes from the Polycythemia Vera Study Group (Berk *et al.*, 1986). This Group, which was established in 1967, conducted a randomized controlled trial with three arms: phlebotomy, chlorambucil and ^{32}P, and 431 patients were randomized to one of these treatments between 1967 and 1974. An analysis conducted in March 1983 showed 10 cases of cancer in the group of 134 patients treated with phlebotomy (two acute leukaemia and eight other cancers), which is comparable with the number expected in the age- and sex-matched general population.

Observational follow-up studies of series of patients with polycythaemia vera and treated with $^{32}PO_4$ show a clear increase in the incidence of acute leukaemia (see Table 64). Precise criteria for the diagnosis of polycythaemia vera were published in 1965 by Modan and Lilienfeld and used in their study. Series of patients in whom polycythaemia vera was diagnosed before that time or a little later (e.g. Fauvert *et al.*, 1961; Osgood, 1964; Halnan & Russell, 1965; Harman & Ledlie, 1967) may have included substantial numbers of patients who did not, in fact, have polycythaemia vera. The incidence of acute leukaemia in series of patients treated with ^{32}P is of the order of

Table 64. Incidences of acute leukaemia in patients with polycythaemia vera treated with $^{32}PO_4$ and by other means

Reference, country, date of treatment or diagnosis	No. of cases/ no. of deaths	Method of treatment, dose	Length of follow-up (years)	No. of cases
Observational studies				
Fauvert *et al*. (1961), France, 1950–1960	194 (143 followed)/ 25 deaths	> 110 MBq $^{32}PO_4$, one or several doses	10	Two acute leukaemias
Osgood (1964), USA, 1947–54	101	Average cumulative dose = 1300 MBq $^{32}PO_4$	> 10	14 acute leukaemias versus 6.5 expected (6 acute granulocytic, 8 acute monocytic)
Halnan & Russell (1965), United Kingdom, 1944–62	107 117	51 GBq $^{32}PO_4$ (total dose) plus X-rays Phlebotomy only	15	No acute leukaemia (0.2 expected); identical survival rate in the two groups
Modan & Lilienfeld (1965), Canada and USA, 1937–53	72 228 79 133	X-rays plus $^{32}PO_4$ $^{32}PO_4$ (dose not reported) X-rays No radiotherapy	8–25	12 acute leukaemias 25 acute leukaemias 7 acute leukaemias 1 acute leukaemia
Szur & Lewis (1966), United Kingdom, date not reported	169	550–2100 MBq $^{32}PO_4$ (total dose)	16	Four leukaemias (3 myelocytic, 1 chronic granulocytic) (2 had also received X-rays and one, chemotherapy)
Harman & Ledlie (1967), United Kingdom, 1948–63	132	$^{32}PO_4$ (dose not reported)	> 10	10 leukaemias (unspecified whether acute)
Tubiana *et al*. (1975), France, 1949–61	303	Average dose, ^{32}P 700 MBq (Landaw, 1976) Once or several times	12–24	50 leukaemias (mostly acute)
Najean *et al*. (1988), France, before 1976	179 64 49	> 85 MBq $^{32}PO_4$ Phlebotomy Chlorambucil or hydroxyurea	> 10	14 ANLL No acute leukaemia 3 ANLL
Randomized controlled trial				
Berk *et al.* (1986), USA, 1967–74	141 156 134	Chlorambucil $^{32}P \leq 185$ MBq per dose Phlebotomy	10–18	19 acute leukaemias 16 acute leukaemias 2 acute leukaemias

ANLL, acute non-lymphocytic leukaemia

10–20% of cases during the 10 years after administration in all the studies (for a review, see Landaw, 1976). Furthermore, in two series (Modan & Lilienfeld, 1965; Tubiana *et al*., 1975), there was a clear dose–response relationship between the frequency of acute leukaemia and the dose of ^{32}P administered. In these observational studies, patients with more severe disease may have been more likely to have been treated with radiation and higher doses.

After 10–18 years of follow-up in the trial of the Polycythemia Vera Study Group (Berk *et al.*, 1986), two cases of acute leukaemia had been reported in 134 patients treated by phlebotomy, 16 cases of acute leukaemia among 156 patients treated with ^{32}P and 19 cases of acute leukaemia plus five cases of large-cell lymphocytic lymphoma among 141 patients treated with chlorambucil (Table 64). Thus there was a clear increase in the incidence of acute leukaemia in the group treated with ^{32}P compared with that treated by phlebotomy. In spite of this, the overall survival of phlebotomy-treated and ^{32}P-treated patients was similar, owing to the complication of thrombosis that affects the former group.

2.8.2 *Other malignancies*

In the series of Modan and Lilienfeld (1965), no significant differences were found in the frequency of non-haematological malignancies between the ^{32}P-treated patients and the group receiving no radiation treatment. In the trial of the Polycythemia Vera Study Group (Berk *et al.*, 1986), an analysis conducted in 1983 suggested excess risks for skin and gastrointestinal cancers in the combined group of patients treated with ^{32}P or chlorambucil when compared with the group treated by phlebotomy. The data for patients treated with ^{32}P were not presented separately.

2.9 Mixed exposures

2.9.1 *Fall-out from atmospheric nuclear weapons testing*

The large collective doses of ionizing radiation committed to the world's population by the nuclear tests are derived mainly from internal exposure to ^{14}C, owing to the long half-life (5730 years) of this radionuclide in large populations, including future generations. The dose rates at which people are exposed to various radionuclides in fall-out are small. The cancer risk attributable to such exposures will be so small that it may not be possible to study a large enough exposed population to detect it.

The thyroid is the most frequently affected organ after exposure to radioactive fall-out close to test sites. The doses to the thyroid from radioactive iodine depend mainly on the consumption of foodstuffs contaminated with ^{131}I and other minor radionuclides deposited on the ground and, to a lesser degree, on inhalation of ^{131}I and ^{133}I. Epidemiological assessment of thyroid cancer attributable to radioactive iodines therefore requires information on individual intake of various contaminated food items and the exposure pathways leading to human intake of the radionuclides. Crude aggregate data

on environmental exposure of populations are a poor measure of internal exposure. Mean population doses can be estimated, taking into account inter-country variations in food consumption and pathways based on aggregate information. Analysis of such data still does not allow for individual variation in doses. This, together with the basic restrictions involved in ecological studies, presents some interpretative limitations.

(*a*) *Nevada test site*

After an early report of a possible increase in the incidence of thyroid cancer (Weiss *et al.*, 1967) at the Nevada test site, where testing of nuclear weapons began in 1951 (see section 1.1.1(*c*)(i)), the Public Health Service of the USA conducted a screening programme in 1965–68 for thyroid disease among several thousand pupils aged 11–18 living in southwestern Utah and adjacent Nevada, who were considered to have been exposed to fresh fission products containing ^{131}I during infancy and childhood in the early 1950s. Of those enrolled, 85–90% participated in the examination. After three years of screening, a cumulative total of 4831 children were examined; 1378 constituted a potentially 'exposed' group on the basis of residence history, and 57 were judged by the panel members to have thyroid nodularity. The prevalence of 13 cases per 1000 for boys and girls combined (14 for boys and 12 for girls) did not differ from that of 14 cases per 1000 among 'unexposed' children in Utah and Nevada (Weiss *et al.*, 1971). In further screening of 5179 children up to 1971, no differences were found in the rates of any category of thyroid disease between exposed and unexposed children (Rallison *et al.*, 1974).

More definitive evidence about thyroid cancer after exposure to fall-out comes from a further follow-up of 4819 (4831 according to Weiss *et al.*, 1971) of the schoolchildren with potential exposure to fall-out (Rallison *et al.*, 1990; Kerber *et al.*, 1993), with an expanded dose reconstruction. Of the individuals who were still living in Arizona, Nevada or Utah, 3122 were re-examined in 1985 and 1986; 2473 subjects were available for analysis. Exposure was assessed from residence history and individual food consumption data obtained by telephone interview. Models were constructed of routes of exposure, including fresh cows' and goats' milk, locally grown vegetables, inhalation and external exposure. Internal doses were estimated by analysis of ^{131}I and ^{133}I intake, taking into account consumption rate, source of milk, feeding patterns, distance from the test site and age. The rates of radionuclide deposition were obtained from the database of the 'Offsite Radiation Exposure Review Project'. The doses to the thyroid ranged from 0 to 4600 mGy (mean, 98 mGy), with a mean of 170 mGy in Utah. Approximately 73% of the exposure of the thyroid to radiation was attributable to milk consumption. During the entire period 1965–86, 56 subjects were found to have 57 thyroid nodules, comprising 11 benign neoplasms, 8 papillary carcinomas, 28 colloid adenomas and 10 non-neoplastic nodules (one subject had both a colloidal adenoma and a papillary carcinoma). The findings constitute a statistically significant excess of thyroid neoplasms (benign and malignant), with a positive dose–response trend. The dose–response relationship for thyroid carcinoma was of marginal significance, largely because of the

small number of cases (Table 65). Potential sources of bias and uncertainty were biased recall of food consumption and uniform application of parameters such as the milk transfer and dose factors to all subjects. [The Working Group noted that the methodological concerns include the fact that the interviewers were aware of the exposure status of the subjects and the apparent over-referral for physical examinations of persons known to reside in the areas with heavy fall-out.] The uncertainty in individual doses was summarized by a geometric standard deviation (a measure of uncertainty independent of dose). After adjustment for the uncertainties resulting from non-differential misclassification, the risk estimate was threefold higher than that without adjustment for uncertainties, while the *p* values remained similar.

The National Cancer Institute (1997) in the USA estimated the ^{131}I doses in counties of the USA and undertook analyses of mortality from and incidence of thyroid cancer in order to determine whether an increased risk for this cancer was related to exposure (Gilbert *et al.*, 1998a). During the period 1957–94, 4602 deaths from thyroid cancer were reported from continental counties, and 12 657 incident cases of thyroid cancer were reported in 1973–94 in selected counties where data on cancer incidence were available. Excess relative risks per Gy were estimated by relating age-, calendar year-, sex- and county-specific rates to the estimated doses to the thyroid adjusted for age at exposure. The risk for thyroid cancer associated with exposure to ^{131}I did not increase with cumulative dose or dose received at the age of 1–15 years, but associations with both mortality and incidence were suggested for individuals who had been exposed when < 1 year of age (Table 66) and with mortality for those born between 1950 and 1959. The authors noted that there was no *a priori* reason to select children under the age of one year for analysis, and the absence of an increase in risk in those aged 1–4 years was not consistent with the results of other studies of external exposure. In addition, the population of the USA is relatively mobile, especially young persons who leave home for university and employment. Thus, it is not clear whether the persons in whom thyroid cancer was diagnosed in the 1980s were living near the Nevada test site in the 1950s when exposure occurred. [The Working Group noted that the contribution to the dose of radiation from nuclear weapons tests by other countries was not taken into account.]

(*b*) *Marshall Islands*

The health of the persons living on three atolls of the Marshall Islands, Rongelap, Ailinginae and Utirik, has been followed since a nuclear explosion, known as the 'Bravo shot', in 1954 (see section 1.1.1(*c*)(ii)). The exposed population originally included 253 inhabitants (Conard *et al.*, 1974; Howard *et al.*, 1997). Since 1955, these persons have undergone a comprehensive, annual physical examination and follow-up examinations at six-month intervals. Between 1964 and 1990, all palpable thyroid nodules were surgically removed. The comparison population comprises 115 inhabitants of Rongelap, age- and sex-matched to the exposed group, who were not on the atoll at the time of the test. By 1957, attrition by emigration required the addition of other unexposed Rongelap

Table 65. Prevalence of thyroid nodules, neoplasms and carcinoma in relation to doses of radiation from fall-out from the test site in Nevada, USA, 1965–86

Dose (mGy)	All nodules			Neoplasms			Carcinoma		
	No. of cases	Rate/ 1000	Adjusted RR (95% CI)	No. of cases	Rate/ 1000	Adjusted RR (95% CI)	No. of cases	Rate/ 1000	Adjusted RR (95% CI)
0–49	29	20.5	1.0	7	4.9	1.0	5	3.5	1.0
50–249	12	18.6	0.9 (0.4–2.1)	3	4.6	0.8 (0.1–6.3)	0	0.0	0.0
250–399	8	33.3	1.9 (0.5–6.1)	5	20.8	2.8 (0.4–22.9)	2	8.3	3.8 (0.2–110.7)
≥ 400	7	41.4	2.3 (0.6–8.0)[a]	4	23.7	3.4 (0.5–26.9)[b]	1	5.9	1.7 (0.1–138.8)[c]
Total	56			19			8		

From Kerber *et al.* (1993); RR, relative risk; CI, confidence interval. RRs adjusted for age, sex and state of residence in 1965
Slope estimate for linear excess RR model (excess RR per mGy):
[a] lower bound = 0.0012 (0.00); $p = 0.16$
[b] lower bound = 0.0070 (0.00074); $p = 0.019$
[c] lower bound = 0.0079 (0.00); $p = 0.096$

Table 66. Estimated excess relative risk (ERR) per Gy of ^{131}I dose by age at exposure for persons exposed in infancy and childhood to fall-out from the test site in Nevada, USA

Age at exposure (years)	Mortality				Incidence (county-specific doses)	
	County-specific doses		State-specific doses			
	ERR/Gy (95% CI)	*p*	ERR/Gy (95% CI)	*p*	ERR/Gy (95% CI)	*p*
< 1	10.6 (–1.1, 29)	0.085	16.6 (–0.2, 43)	0.054	2.4 (–0.5, 5.6)	0.11
< 5	1.5 (< 0, 5.7)	0.35	2.7 (–1.1, 8.4)	0.19	–0.1 (–0.8, 0.8)	0.89
< 15	–0.2 (< 0, 1.6)	0.79	0.1 (–1.6, 2.3)	0.92	–0.3 (–0.8, 0.2)	0.22

From Gilbert *et al.* (1998a). ERR, excess relative risk; CI, confidence interval

inhabitants to provide an adequate number of people for the comparison group; the total comparison group eventually examined consisted of 227 individuals. The small size of the exposed population and uncertainty about the radionuclides present make it difficult to evaluate the risks for cancer and other diseases associated with fall-out in this population. However, the follow-up data are of interest, and the incidences of thyroid nodules and cancer have been reported up to 1986 (Table 67). Nine cases of papillary carcinoma of the thyroid were diagnosed among 253 exposed individuals, and two were found among 227 unexposed individuals (2.1 expected for unexposed Marshallese). With the doses estimated by Lessard *et al*. (1985), the risk coefficient for thyroid cancer was 1.5 per 10^6 persons per cGy per year. This estimate is uncertain, primarily because of the lack of precise data on the radionuclides involved. The interpretation is complicated by the possibility of hypothyroid conditions existing before exposure (which would have enhanced the uptake of radioactive iodine) and the use of thyroxine therapy to lower thyroid-stimulating hormone concentrations in the Rongelap inhabitants after exposure (Robbins & Adams, 1989).

(*c*) *Other test sites*

Few epidemiological data are available on cancers and exposure to fall-out from other nuclear test sites. Excess risks for thyroid cancers in regions adjacent to the Semipalatinsk test site in eastern Kazakhstan (see section 1.1.1(*c*)(iii)) have been suggested, but their relationship to radiation is unclear (Peterson *et al*., 1998). [The Working Group noted that the data are difficult to interpret because of potential bias in the selection of patients treated in hospitals and the lack of data on the population from which the cases came.]

The findings with regard to leukaemia among persons exposed during atomic weapons testing are described in the first monograph on ionizing radiation (IARC, 2000).

Table 67. Thyroid nodules and cancer in inhabitants of Rongelap atoll, Sifo Island (Ailinginae atoll) and Utirik atoll in the Marshall Islands through 1986

Site	Age at exposure (years)	No. of persons	Thyroid nodules		Thyroid cancer	
			No. observed	No. expected	No. observed	No. expected
Rongelap	*In utero*	3	2	0.079	0	0.026
	< 10	21	15	0.50	1	0.17
	10–18	12	3	0.92	2	0.15
	> 18	31	3	2.7	2	0.21
Sifo	*In utero*	1	0	0.026	0	0.0087
	< 10	7	2	0.18	0	0.061
	10–18	0	–	–	–	–
	> 18	11	3	0.98	0	0.075
Utirik	*In utero*	8	0	0.21	0	0.070
	< 10	56	8	1.5	1	0.49
	10–18	19	7	1.4	2	0.24
	> 18	84	8	7.5	1	0.58
All exposed		253	51	16	9	2.1
Comparison[a]		227	10		2	

From Robbins & Adams (1989). The expected numbers were based on those for unexposed Marshallese, as reported by Lessard *et al*. (1985).

[a] Age- and sex-matched unexposed Rongelap inhabitants, including additions to replace those lost to follow-up

2.9.2 *Techa River, Russian Federation*

The Techa River flows for about 240 km through the southern Ural Mountains. The history and dosimetry of exposure of the surrounding population to radionuclides from the Mayak facility is described in section 1.1.2(*b*), and the carcinogenic effects of exposure to plutonium are summarized in section 2.4.3. During 1949–56, radioactive wastes were discharged directly into the Techa River, and almost 124 000 people living on the banks of the Techa and Iset rivers received internal exposure (from ingestion of ^{89}Sr, ^{90}Sr and ^{137}Cs in contaminated water and food) and external exposure (from ^{137}Cs, ^{106}Ru, ^{95}Zr and other radionuclides) (Kossenko & Degteva, 1994; Kossenko, 1996; Yachmenyov & Isageva, 1996; Kossenko *et al*., 1997). Of the radionuclides released into the Techa River, the main contributor to internal exposure was ^{90}Sr, which accumulates in bone tissues and remains there for many years. In order to study the possible late effects of this exposure, a cohort of nearly 30 000 people was identified in 1968 from tax and medical records and evacuation lists, consisting of all persons who had been living in defined areas near the River on 1 January 1950.

A follow-up study of mortality (Kossenko *et al.*, 1997) suggested that the risks for death from leukaemia and other cancers had increased with increasing radiation dose in this population (Table 68). The dose categories were defined in terms of the estimated committed soft-tissue dose for solid tumours and the committed bone-marrow dose for leukaemia [apparently until the end of follow-up]. The excess numbers of cases were estimated as the difference between the observed number and an estimate of the number expected in the absence of exposure. The latter figure was calculated on the basis of an internal analysis of persons exposed to different doses, and appropriate external rates were not used. As significant external exposure was also received as a consequence of the release of radionuclides into the Techa River (Degteva *et al.*, 2000a,b), it is difficult to distinguish the independent effects of the internal and external exposures.

Table 68. Deaths from leukaemia and solid cancers in the Techa River cohort, 1950–89

Dose category (Sv)	Leukaemia			Solid tumours		
	Person–years	Observed	Excess	Person–years	Observed	Excess
0.005–0.1	103 031	3	–1	459 576	716	5
0.1–0.2	194 858	13	4	96 297	126	1
0.2–0.5	200 144	16	6	19 582	34	10
0.5–1	93 873	9	5	32 204	52	6
> 1	49 398	9	7	33 645	41	8
Total	641 304	50	21	641 304	969	30

Adapted from Kossenko *et al*. (1997). Person–years computed through date of death, loss to follow-up or 31 December 1989

The Techa River cohort is important because it consists of a general population (both sexes and all ages) exposed to a wide range of doses. The population living in the affected settlements includes members of two distinct ethnic groups, Russian and Tatar/Bashkir, so that ethnic differences in cancer risk might be studied. Kossenko *et al*. (1997) noted a number of limitations of their study, including difficulties in dosimetry, incomplete ascertainment of vital status and the absence of a fixed internal control group. There may also have been possible confounding from the presence of toxic chemicals in the liquid wastes released from the Mayak facility (UNSCEAR, 1994, 2000). [The Working Group noted that the adequacy of the dose estimates and the completeness of follow-up in this study are being investigated.]

2.10 Caesium

Fall-out from weapons testing in the 1950s and from the Chernobyl accident resulted in the ingestion of ^{137}Cs by Lapps who breed reindeer in the northern parts of the Nordic countries and the Russian Federation (Ahman & Ahman, 1994). In addition, small amounts of ^{241}Am and ^{241}Pu were ingested by Lapps from contaminated reindeer (Holm & Persson, 1978).

A cohort of 2034 Lapps who bred reindeer in Sweden or who were members of the households of breeders was assembled in 1960 and followed through mortality registries from 1961 through 1985. The rate of mortality from all causes was similar to that of the entire Swedish population: 428 deaths occurred, and the SMR was 0.95. A significantly lower mortality rate than expected was observed for all cancers (SMR, 0.70), and significantly decreased risks were found for cancers of the colon, respiratory organs, female breast, male genital organs and kidneys and for malignant lymphomas. The stomach was the only site for which a significantly increased risk for cancer was found (SIR, 2.25; 95% CI, 1.46–3.32) when compared with national rates. Lapps who breed reindeer have ingested fall-out products via the lichen–reindeer–man food chain since the 1950s, but no increased risk was found for cancers at the sites considered to be most sensitive to radiation (Wiklund *et al*., 1990, 1991).

2.11 Low-energy β-particle-emitting radionuclides

Several radionuclides that emit low-energy β-particles can be deposited in the body, where they act as internal emitters. Examples are ^{3}H (18.6 keV) and ^{14}C (156.5 keV) (see section 2.9.1). Both are pure β-particle emitters with stable decay products. The doses from ^{3}H are included in the dosimetry of whole-body external radiation for workers. In a case–control study of prostate cancer among workers at the Atomic Energy Authority in the United Kingdom, Rooney *et al*. (1993) found a significant association with the probable level of exposure to ^{3}H (χ^2 for trend, 5.9; $p < 0.05$; 1 degree of freedom); however, the ^{3}H-exposed workers were also exposed to external γ-radiation and a number of other radionuclides.