INTERNALIZED α-PARTICLE EMITTING RADIONUCLIDES

Internalized radionuclides that emit α-particles were considered by a previous IARC Working Group in 2000 (IARC, 2001). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

See Section 1 of the *Monograph* on X-radiation and γ-radiation in this volume.

2. Cancer in Humans

2.1 Radon

Radon is a natural radioactive gas produced by the decay of uranium and thorium, which are present in all rocks and soils in small quantities. There are several isotopes of radon, the most important of which are ^{222}Rn (produced from ^{238}U) and ^{220}Rn (produced from thorium). ^{220}Rn is also known as thoron because of its parent radionuclide. In the United Kingdom, it has been shown that ^{220}Rn delivers much smaller doses to the public in indoor environments than ^{222}Rn (The Independent Advisory Group on Ionising Radiation, 2009). Unlike ^{222}Rn, ^{220}Rn is not formed during the radioactive decay of ^{238}U, and is hence not present at appreciable levels in uranium mines.

The epidemiological evidence on the cancer risks from radon is derived largely from cohort studies of underground miners that had been exposed to high levels of radon in the past. More recently, a series of case–control studies of lower exposures to residential radon have also been conducted.

The previous *IARC Monograph* on radon IARC (1988) states that radon is a cause of lung cancer in humans, based on clear excess lung cancer rates consistently observed in underground miners, and elevated lung cancer risks seen in experimental animals exposed to radon. In a subsequent evaluation by IARC (2001), additional epidemiological evidence of an increased lung cancer was also seen in case–control studies of residential radon. Although results from the 13 case–control studies available at that time were not conclusive, the Working Group noted that the risk estimates from a meta-analyses of eight such studies were consistent with estimates based on the underground miner data (Lubin & Boice, 1997).

In a detailed evaluation of the health risks of radon by the Committee on the Biological Effects of Ionizing Radiation (BEIR) within the

US National Research Council (BEIR IV, 1988), it was also reported that radon is a cause of lung cancer in humans. An important aspect of this work was the development of risk projection models for radon-related lung cancer, which provides estimates of the lung cancer risk associated with residential radon, depending on age, time since exposure, and either concentration or duration of exposure.

In an effort to synthesize the main epidemiological findings and assist in the evaluation of the lung cancer risks associated with occupational and environmental exposure to radon, several combined analyses of the primary raw data from studies of radon and lung cancer have been conducted. Several combined analyses of epidemiological data from 11 cohorts of underground miners have been conducted (BEIR IV, 1988; Lubin *et al.*, 1994; Lubin & Boice, 1997; BEIR VI, 1999). Howe (2006) conducted a combined analysis of data from three cohorts of uranium miners from Canada, and Tomášek *et al.* (2008) conducted a combined analysis of Czech and French uranium miners. Combined analyses of epidemiological data from seven North American case–control studies of residential radon and lung cancer (Krewski *et al.*, 2005), 13 European studies (Darby *et al.*, 2005, 2006), and two studies from the People's Republic of China (Lubin *et al.*, 2004) have also been conducted.

Cancers other than lung cancer, notably haematopoietic lesions, have been investigated in some of the cohort studies of miners. Case–control studies of residential radon and childhood cancers, including leukaemia, have also been conducted. Ecological studies of environmental radon and the risk of lung and other cancers have been reported, but these are less informative than the cohort and case–control studies discussed previously (IARC, 2001).

2.1.1 Occupational studies of underground miners

(a) Early observations of lung disease in miners

Underground mining was the first occupation associated with an increased risk of lung cancer. Metal ores were mined in the Erz mountains (a range between Bohemia and Saxony), in Schneeberg from the 1400s and in Joachimsthal (Jachymov) from the 1500s. As early as the 16th century, Georg Agricola, in his treatise 'De re Metallica', described exceptionally high mortality rates from respiratory diseases among miners in the Erz mountains. The disease in miners was recognized as cancer in 1879 by Harting & Hesse (1879). This report provided clinical and autopsy descriptions of intrathoracic neoplasms in miners, which were classified as lymphosarcoma. During the early 20th century, histopathological review of a series of cases established that the malignancy prevalent among miners in the Erz mountains was primary cancer of the lung (Arnstein, 1913; Rostocki, 1926). Many authors offered explanations for this excess including exposures to dusts or metals in the ore (particularly arsenic). In 1932, Pirchan and Sikl suggested that radioactivity was the most probable cause of the cancers observed in Jachymov (Pirchan & Sikl, 1932).

(b) Cohort studies

The first epidemiological evidence of an increased lung cancer risk among underground miners exposed to radon in the Colorado Plateau was given by Archer *et al.* (1962). Subsequent analyses of this cohort were conducted by Wagoner *et al.* (1964, 1965) as additional lung cancer cases accrued; the latter analysis was the first to relate lung cancer risk to cumulative exposure to radon progeny in terms of working-level months (WLM). Stram *et al.* (1999) conducted detailed analyses of the effects of uncertainties in radon exposures within this cohort on radon-related lung cancer risk estimates. Another early study reported

lung cancer risk in Canadian fluorspar mines in Newfoundland, where substantial amounts of water seeping through the mines contain radon gas (de Villiers, 1966). The first statistical study on the incidence of lung cancer among uranium miners from former Czechoslovakia (the Czech Republic) was published in 1966 by (Rericha *et al.*, 1966), followed by results on autopsy-verified lung cancer cases (Horacek, 1968). The first epidemiological study in uranium miners from former Czechoslovakia (the Czech Republic) was initiated in the late 1960s, with first results reported shortly thereafter (Sevc *et al.*, 1971). In contrast to other epidemiological studies, there were hundreds of radon measurements per year in every mine. As of now, cancer risks in 19 cohorts of underground miners exposed to radon have been investigated (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.1.pdf). In each of these cohorts, occupational exposure to radon decay products was associated with increased lung cancer risk.

To increase statistical power, particularly in quantifying the modifying effect of different factors related to time or age, attempts were made to pool individual data from related studies for the joint estimation of risk and the evaluation of modifying factors. The first such analyses were conducted by the BEIR IV committee (BEIR IV, 1988), and included a combined analysis of three studies of uranium miners in the Colorado Plateau, USA, the Eldorado mine in Ontario, Canada, and Swedish iron miners in Malmberget.

By building on initial work by Lubin *et al.* (1994, 1995) and Lubin & Boice (1997), a subsequent report by the US National Research Council (Lubin, 2003) extended the combined analysis to encompass 11 cohorts of underground miners (see Table 2.1 on-line). An important aspect of this analysis was the development of a comprehensive risk model for radon-induced lung cancer in underground miners taking into account age, time since exposure, and either exposure concentration or duration of exposure (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.2.pdf). The previous risk model developed by the BEIR IV committee did not consider exposure concentration or duration. The BEIR VI risk models indicated that lung cancer risk decreased with time since exposure and age; for a fixed cumulative exposure, the risk decreased with increasing exposure concentration (reflecting an inverse exposure–rate effect), and increased with duration of exposure.

Another pooled analysis was conducted in a joint cohort of Czech and French uranium miners, including a total of 10100 miners and 574 lung cancers (Tomášek *et al.*, 2008). Cohort members were subject to relatively low levels of radon exposure (mostly below 4 working-level (WL)); exposure measurements were available for over 96% of the total exposure time experienced by individuals in this joint cohort. The effect of the quality of the exposure data in this joint study was analysed by distinguishing exposures based on measurements from those that were estimated or extrapolated. If exposure quality is not accounted for, the estimated ERR/WLM is substantially underestimated by a factor of 3.4 in the French study; however, effect modification by exposure quality was not observed in this study with relatively low annual exposures, for which measurements were almost always available. The term ERR/WLM quantifies the increased in risk per exposure in working-level months. More specifically, WLM is a time-integrated exposure measure, and it is the product of the time in working months (170 hours) and working-level. One WL equals any combination of radon progeny in 1 litre of air that gives the ultimate emission of 130000 MeV of energy of α-particles. Consequently, 1 WLM corresponds to 2.08×10^{-5} J/m^3 x 170 hours = 3.5×10^{-3} J-hours/m^3.

Predictions of lung cancer risk were not substantially different from those based on the BEIR VI risk models (Table 2.2 on-line). [The

Working Group noted that a complicating factor in the interpretation of data on lung cancer risks among uranium miners from former Czechoslovakia (the Czech Republic) is the joint exposure to γ-radiation, which can also increase lung cancer risk.]

In contrast to the empirical radon risk projection models developed by the BEIR IV committee, the BEIR VI committee (BEIR VI, 1999) applied biologically based risk models to describe the lung cancer risks relation to radon in the Czech and French cohorts; a discussion on the interpretation of risk projections derived from the application of such models to epidemiological data on radon is provided in Heidenreich & Paretzke (2004).

Grosche *et al.* (2006) reported on a new German cohort of 59000 uranium miners, with 2388 lung cancer cases. This is the largest of the miner cohorts investigated to date, and is comparable in size to the 11 cohorts considered in the BEIR VI report combined (BEIR VI, 1999). Patterns of risk based on age and exposure concentration were similar to those found in the BEIR VI report (BEIR VI, 1999), although the effect of time since exposure was somewhat different (Table 2.2 on-line), possibly reflecting the higher proportion of missing causes of death in the early years of follow-up. Howe (2006) conducted a combined analysis of Canadian data on uranium miners from the Beaverlodge, Port Radium, and Port Hope cohorts. The study included 17660 workers, with 618 cases of lung cancer. Patterns of lung cancer risk were similar to those found in the BEIR VI report (Table 2.2 on-line).

(c) *Joint effects of radon and smoking on lung cancer risk*

Because tobacco smoking is a powerful risk factor for lung cancer, the joint effects of radon and smoking need to be considered. The interactions between exposure to radon and smoking in the six studies of miners for which smoking information was available were investigated by Lubin *et al.* (1995). Although some studies were consistent with additive effects of radon and tobacco smoke on lung cancer risk, other interactions between radon and tobacco smoke in which the joint effects of these two agents were greater than additive (Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.3.pdf). Six of the above studies were jointly analysed in the BEIR VI report (BEIR VI, 1999), which suggested a submultiplicative model. The ratio of ERR/WLM in non-smokers and smokers was 3.0 (95%CI: 0.3 – 29.2). [The Working Group noted that the confidence interval of this ratio was relatively wide, because of the small numbers of lung cancers (64) among non-smokers.] In these studies, the radon risk coefficients adjusted for smoking were not substantially different from those obtained when smoking was ignored.

(d) *Lung cancer risks among haematite miners*

Previous *IARC Monographs* have implicated radon as contributing to the excess lung cancer risk observed in haematite miners (IARC, 1972, 1987, 1988). Volume 43 of the *IARC Monographs* (IARC, 1988) states that "underground haematite mining with exposure to radon is carcinogenic to humans." Lawler *et al.* (1985) noted no increased mortality in 10403 lung cancer among miners in Minnesota haematite mines relative to population rates (SMR, 1.00) with low-grade exposure to radon daughters and silica dust. Kinlen & Willows (1988) noted that other iron mines, like that in Cumbria in the United Kingdom, in which 864 underground miners were studied, the SMR for lung cancer among workers was increased relative to population rates in the period 1948–67 (SMR, 1.53), but not thereafter (SMR, 1.13). Radon levels in early periods were in the range of 0.35–3.2 WL, and decreased to

0.1–0.8 WL, suggesting that radon was the causative agent. In a study of 5406 haematite miners in China, a significant excess of lung cancer (SMR, 3.7) was observed, although this was based on only 29 cases of lung cancer (Chen *et al.*, 1990). In this study, lung cancer risk increased notably with increasing radon concentrations and with increasing dust concentrations; however, the authors were unable to evaluate the independent effects of radon and dust, because these two hazards were positively correlated. Collectively, these observations provide evidence that radon increases the risk of lung cancer in haematite miners.

(e) Leukaemia risks in miners

Health effects of exposure to radon progeny other than lung cancer, including leukaemia, have been addressed in several miner studies (see Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.4.pdf). A combined analysis of 11 cohorts of underground miners showed no evidence of an increased risk of leukaemia (Darby, 1995). However, significant trends in the risk of leukaemia were found in the Czech study in relation to duration of exposure (Tomášek *et al.*, 1993; Tomášek & Zárská, 2004), and to cumulative joint exposure to radiation from radon gas, external sources of exposure to γ-radiation, and long-lived radionuclides (Tomášek & Kubik, 2006). In a separate Czech cohort, the risk of leukaemia also increased with cumulative radon exposure (Rericha *et al.*, 2006). Another analysis of a large German cohort of uranium miners has shown a significant increase in the incidence of leukaemia among the highest exposed miners (Möhner *et al.*, 2006), although leukaemia mortality was not associated with exposure to radon progeny (Kreuzer *et al.*, 2008).

(f) Cancers other than lung and leukaemia

Darby *et al.* (2005) found no evidence of an increased risk of other cancers in their pooled analysis of 11 miner cohort studies. In an analysis of the large German cohort, Kreuzer *et al.* (2008) found a statistically significant relationship between cumulative radon exposure and mortality from all extra pulmonary cancers combined; this result persisted after adjustment for potential confounding by arsenic, dust, long-lived radionuclides and γ-radiation. Increasing trends in cancer risk were also reported at several specific sites in this study; however, none of these trends was significant after adjustment for potential confounding.

Sevcová (1989) reported that the risk of basal cell carcinoma among Czech uranium miners was 2–12 times higher than in the general male population. The mean equivalent dose in the basal layer of epidermis was estimated to be 0.6–5.0 Sv, depending on the duration of exposure (Sevcová *et al.*, 1978). Based on 27 cases observed during a 20-year follow-up period, the ERR/Sv was estimated to be 2.2 (Sevcová, 1989).

2.1.2 Environmental studies of indoor radon

An extensive set of case–control studies of indoor radon and lung cancer were designed, and, taken individually, these studies did not provide conclusive evidence of an association between indoor radon exposure and lung cancer risk. Because of the difficulty in identifying the comparatively small relative risks that would be anticipated from indoor radon exposure, combined analyses of these studies were undertaken in North America, Europe and China (see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.5.pdf). The combined analyses had inclusion criteria for each study with clear rules for the selection of persons with lung cancer that included the following: the selection of controls

so as to be representative of the population from which the lung cancer cases arose; the availability of detailed residential histories, compiled in a similar way both for cases and controls; the availability of long-term (minimum 2 months) measurements of radon gas concentrations; and availability of data on smoking habits for individual study subjects.

(a) Combined analysis of North American case–control studies

The combined analysis of seven North American case–control studies included a total of 3662 cases and 4966 controls (Krewski *et al.*, 2005, 2006). All studies used long-term α-particle track detectors to measure the concentration of radon progeny in indoor air for 12 months (Field *et al.*, 2006). Contemporaneous measurements were made in homes that subjects had occupied or were currently occupying; these measurements were used to estimate historical radon concentrations in those homes. Detectors were placed in the living areas and bedroom areas of the home in which subjects had spent the majority of their time. Conditional likelihood regression was used to estimate the excess risk of lung cancer. Table 2.6 (available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.6.pdf) shows the estimated odds ratios for lung cancer by different concentration levels of radon, and the excess odds ratios per 100 Bq/m^3. Odds ratios for lung cancer increased with residential radon concentration. The estimated odds ratio after exposure to radon at a concentration of 100 Bq/m^3 in the exposure time window of 5–30 years before the index date was 1.11 (95%CI: 1.00–1.28). This estimate is compatible with the estimate of 1.12 (95%CI: 1.02–1.25) predicted by downward extrapolation of the miner data.

The examination of potential effect modification by demographic factors (sex, age, education level, respondent type) and smoking variables (smoking status, number of cigarettes per day, duration of smoking, years since quitting smoking) showed no evidence of heterogeneity of radon effects. There was no apparent heterogeneity in the association by sex, educational level, type of respondent (proxy or self), or cigarette smoking, although there was some evidence of a decreasing radon-associated lung cancer risk with age ($P = 0.23$).

Analysis of the effects of radon exposure by different histological types of lung cancer showed the largest excess odds ratio (0.23 per 100 Bq/m^3) for small cell carcinoma, although the confidence limits overlapped with other histological types of lung cancer. Because of the reduced number of subjects, all of the confidence limits for the excess odds ratios for specific histological types of lung cancer included zero. Analyses restricted to subsets of the data with presumed more accurate radon dosimetry (increasing number of years in the 5–30 exposure time window and limiting the number of residences by subjects) resulted in increased estimates of risk with increasing number of years monitored. In addition, excess odds ratios were larger when data were restricted to subjects living in one or two houses compared with no housing restrictions. These results provide direct evidence of an association between residential radon exposure and lung cancer risk.

(b) Combined analysis of the European case–control studies

Combined analysis of case–control studies of indoor radon have also been carried out in Europe. Darby *et al.* (2005, 2006) pooled individual data from all studies and organized them into a uniform data format to more precisely estimate the increased risk of lung cancer due to residential radon exposure, and to determine the modifying effects of smoking, age, sex, and other factors.

Data on smoking history and also on radon exposure history, based on long-term measurements of radon gas concentrations, were available for a total of 7148 persons with lung cancer

and 14208 controls. Among the people with lung cancer, the mean time-weighted observed average residential radon concentration during the 30-year period ending 5 years before diagnosis was 104 Bq/m^3. The ratio of the number of controls to the number of cases differed between the different studies, and the time-weighted average observed residential radon concentration for the controls, with weights proportional to the study-specific numbers of cases, was 97 Bq/m^3. The association between the risk of developing lung cancer and residential radon concentrations in these data was studied using linear models for the relative risk, with stratification for study, age, sex, region of residence within each study, and detailed smoking history. Analyses were carried out first in relation to the observed radon concentration without making any adjustment for the effect of uncertainties in the assessment. The major analyses were then repeated with an approximate adjustment to take into account uncertainties in radon concentrations.

This combined analysis showed that there was clear evidence (P = 0.0007) of an association between the residential radon concentration during the previous 35 years and the risk of lung cancer. The dose–response relationship was linear, and the estimated ERR of lung cancer was 0.08 (95%CI: 0.03–0.16) for a 100 Bq/m^3 increase in the time-weighted average observed radon concentration. This corresponds to an increase of 0.16 (95%CI: 0.05–0.31) per 100 Bq/m^3 increase in usual radon; that is, after correction for the dilution caused by random uncertainties in measuring radon concentrations. The proportionate excess risk did not differ significantly with study, age, sex, or smoking. The dose–response relationship seemed to be linear with no threshold, and remained significant (P = 0.04) in analyses limited to individuals from homes with measured radon concentrations < 200 Bq/m^3. There was no evidence that the dose–response relationship varied between the different studies (P = 0.94), nor were the results dominated by any individual study.

Analysis of radon effects by histological types of lung cancer showed a stronger and statistically significant dose–response relationship with small cell cancer. For squamous cell carcinoma, the estimated value of β was slightly negative, while for adenocarcinoma and for other confirmed histological types, it was positive. However, in all these later three groups the 95% confidence interval for β included zero. [The Working Group noted that not all studies contributed to this analysis.]

Correction for the effects of random uncertainties in the assessment of radon concentrations were made using data on repeat radon measurements in the same home. These corrections resulted in the relative risk per 100 Bq/m^3 nearly doubling from 0.084 to 0.16, with the width of the associated 95% confidence interval increasing from 0.030–0.158 to 0.05–0.31 (Krewski *et al.*, 2005). [The Working Group noted that a similar effect was seen in the North American studies when combined analyses were restricted to data for which the most complete radon dosimetry was available.]

(c) Combined analysis of studies in China

Data from the two studies of residential radon representing two large radon studies conducted in China were combined and analysed (Lubin *et al.*, 2004). The studies included 1050 lung cancer cases and 1996 controls. In the pooled data, odds ratios increased significantly with greater radon concentration. Based on a linear model, the odds ratio was 1.33 (95%CI: 1.01–1.36) at radon exposure levels of 100 Bq/m^3. For subjects who lived in a home for 30 years or more, the odds ratio at 100 Bq/m^3 was 1.32 (95%CI: 1.07–1.91).

(d) Ecological studies of residential radon and lung cancer

Cohen & Colditz (1995) reported a negative correlation between radon levels and lung cancer in over 3000 counties in the USA. Such ecological studies are subject to several limitations, including the absence of county-specific data on smoking, which can confound the association between ecological indicators of radon exposure and lung cancer risk. This possibility was confirmed by (Puskin, 2003), who subsequently reported that negative correlations were obtained between county-level radon concentrations and county-level cancer occurrence rates for cancers known to be related to tobacco smoking, with no correlation at the ecological level between radon and cancers not related to tobacco smoking. Similarly, Lagarde & Pershagen, (1999) demonstrated that an increasing trend in lung cancer risk with increasing exposure to indoor radon observed in a national Swedish case–control study became a decreasing trend when information on radon and lung cancer was aggregated to the ecological (county) level.

(e) Attributable risk of lung cancer

Darby *et al.* (2005) estimated the fraction of the lung cancer burden attributable to indoor radon in Europe to be about 9%, based on the relative risk of lung cancer associated with exposure to indoor radon in the combined analysis of the 13 European case–control studies, and the indoor radon concentrations observed in those studies. In the USA, the BEIR VI committee (BEIR VI, 1999) used the radon risk projection models developed on the basis of the miner data, and data on radon concentrations in US homes to estimate the attributable fraction to be in the range of 10–15%, depending on which of the committee's two preferred risk models was used. Brand *et al.* (2005) used the BEIR VI risk models and data on radon concentrations in Canadian homes to obtain an estimate of the attributable fraction of 8%. Although subject to some uncertainty, these results suggest that about 8–15% of the lung cancer deaths in Europe and North America may be attributed to residential radon exposure, making radon the second leading cause of lung cancer death after tobacco smoking in those regions.

(f) Studies of leukaemia

Lubin *et al.* (1998) conducted a case–control study of acute lymphoblastic leukaemia among children under 15 years of age in the USA in relation to residential radon exposure (see Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.7.pdf), based on 1-year track-etch radon measurements in all current and previous residences in which they had lived for at least 6 months. This study provided no evidence of an association between indoor radon exposure and childhood acute lymphoblastic leukaemia. In a subsequent case–control study of leukaemia and central nervous system (CNS) tumours (nephroblastoma, neuroblastoma, and rhabdomyosarcoma), Kaletsch *et al.* (1999) found no evidence of an increased risk of leukaemia of children under 15 years of age in Lower Saxony, Germany. Steinbuch *et al.* (1999) reported no increase in the risk of acute myeloid leukaemia of children under 18 years of age identified through the Children's Cancer Group, which involves over 120 institutions in the USA and Canada. Law *et al.* (2000a) did not find evidence of an increased risk of either acute lymphoblastic leukaemia or acute myeloid leukaemia in adults 16–69 years of age in the United Kingdom. Results from the United Kingdom Childhood Cancer Study, which included 805 cases of acute lymphoblastic leukaemia, demonstrated no association between residential radon and leukaemia (Cartwright *et al.*, 2002). Raaschou-Nielsen (2008) conducted a case–control study of 2400 cases of leukaemia, CNS tumours, and malignant lymphoma in children under 15 years of age identified through

the Danish Cancer Registry. Cumulative radon exposure was associated with an increased risk of acute lymphoblastic leukaemia, with an odds ratio of 1.63 (95%CI: 1.05–1.23) for children exposed to more than 890 Bq/m^3–years, relative to children exposed to less than 160 Bq/m^3–years. [The Working Group noted that a strength of this study was the inclusion of virtually all relevant cases in Denmark.]

Several ecological studies and surveys suggested a positive correlation between exposure to indoor radon and the risk of adult acute leukaemia (especially myeloid leukaemia) and childhood leukaemia (Henshaw *et al.*, 1990; Haque & Kirk, 1992; Kohli *et al.*, 2000; Evrard *et al.*, 2006). These studies were based on an ecological design in which radon levels were regressed against the incidence of several cancer sites. Average radon concentrations were obtained from national or county surveys, and recorded as population-averaged arithmetic means. In some cases, crude geographic or geological features of the inhabited areas were used to derive estimates of levels of radiation emission, and subsequently used as surrogates for exposure assessment (Forastiere *et al.*, 1992). [The Working Group noted that this type of study design has many limitations, including a lack of measurement of individual exposure to indoor radiation, a lack of control population, the difficulty in separating radon effect from that of indoor γ-radiation, and the absence of multiple regression analyses of potential confounders (Eatough & Henshaw, 1994). In addition, ecological studies were often based on the assumption that national or regional radon concentrations apply to areas where cancer registries have been compiled.]

(g) Cancers other than lung and leukaemia

In addition to leukaemia, the case–control study conducted by (Kaletsch *et al.*, 1999) in Germany examined the association between indoor radon and solid tumours. An elevated odds ratio of 2.61 was reported (95%CI: 0.96–7.13) for radon exposures above 70 Bq/m^3 relative to lower exposures; and this finding was based mainly on six CNS tumours, for which the odds ratio was 3.85 (95%CI: 1.26–11.81). The United Kingdom Childhood Cancer Study examined the association between indoor radon and non-Hodgkin lymphoma, Hodgkin disease, CNS tumours, and other solid tumours, and found no association with any of these tumours (Cartwright *et al.*, 2002). The case–control study by Raaschou-Nielsen (2008) in Denmark found no association between indoor radon and either tumours of the central nervous system or malignant lymphoma.

Ecological studies have suggested that several cancers might also be weakly correlated with indoor radon, especially kidney cancer, prostate cancer, malignant melanoma, and some childhood cancers (Butland *et al.*, 1990; Axelson, 1995). However, these studies use ecological indicators of radon exposure, and do not control for possible confounders such as indoor γ-radiation or tobacco smoking.

2.1.3 Synthesis

Cohort studies of underground miners exposed to high levels of radon (specifically, ^{222}Rn and its decay products) in the past have consistently demonstrated an increased risk of lung cancer, providing *sufficient evidence* of carcinogenicity in humans (IARC, 1988). Case–control studies of residential radon and lung cancer have added to the weight of epidemiological evidence linking radon to lung cancer (IARC, 2001).

Since then, combined analyses of data from seven case–control studies of indoor radon and lung cancer in North America (Krewski *et al.*, 2005, 2006), 13 case–control studies in Europe (Darby *et al.*, 2005, 2006), and two studies in China (Lubin *et al.*, 2004) have provided clear evidence of an increased risk of lung cancer due to radon (specifically, ^{222}Rn and its decay products) in homes. A large study of uranium miners in

Germany (Grosche *et al.*, 2006) and a joint study in France and the Czech Republic (Tomášek *et al.*, 2008) have reaffirmed previous findings of increased risk of lung cancer in underground miners exposed to radon.

Cohort studies of underground miners permit an assessment of cancer risk at multiple sites; and some evidence of an increased risk of leukaemia was reported among Czech uranium miners, although these miners were also exposed to γ-radiation (a risk factor for leukaemia). Case–control studies of childhood and adult leukaemia in relation to indoor radon exposure have mostly not shown elevated risks, although one study suggested an increased risk of leukaemia among children in Denmark. An increased risk of solid tumours was seen in one case–control study in Germany; however, this result was based on only six CNS tumours, and was not confirmed in other case–control studies.

IARC (1972, 1987, 1988) previously concluded that haematite miners exposed to radon were at increased risk of lung cancer. A subsequent study of haematite miners in China demonstrated increasing lung cancer risk with increasing radon concentrations; however, a similar trend was seen with increasing dust concentrations, and it was not possible to separate the effects of radon and dust in this study. The Working Group reaffirmed the conclusion reached in the earlier IARC evaluations that radon contributes to the increased lung cancer risk seen in haematite miners.

2.2 α-Particle emitters

2.2.1 Radium-224/226/228

The previous *IARC Monograph* evaluation of radium-224, radium-226, and radium-228 IARC (2001) was based on an increased risk of bone sarcoma associated with all three isotopes, as well as an increased risk of paranasal sinuses and mastoid process associated with ^{226}Ra, in cohorts of radium watch-dial painters who ingested ^{226}Ra (often in combination with ^{228}Ra), and patients injected with ^{224}Ra. Few epidemiological analyses of cancer risk following radium exposure have been published since then. One of these is an update to a cohort study of patients injected with ^{224}Ra in Germany (Wick *et al.*, 2008), while two recent case–control studies in the USA and Thailand have considered radium in drinking-water (Guse *et al.*, 2002; Hirunwatthanakul *et al.*, 2006).

(a) Bone

The cohort studies of cancer risk among radium watch-dial painters in the USA were initially carried out at the Massachusetts Institute of Technology (Rowland *et al.*, 1978) and the Argonne National Laboratory (Stebbings *et al.*, 1984; Carnes *et al.*, 1997), and later combined (Rowland *et al.*, 1983; Spiers *et al.*, 1983). Those studies, in which some of the painters ingested ^{226}Ra (often in combination with ^{228}Ra) by the practice of 'pointing' their paintbrush tips with their lips, showed consistent increases in the risk for bone sarcoma related to exposure to α-particles (Rowland *et al.*, 1978; Stebbings *et al.*, 1984; see Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.8.pdf). Carnes *et al.* (1997) reported that both isotopes of radium contributed significantly and independently to the rate of mortality from bone sarcomas in multivariate analyses of dose–response relationships in which the two isotopes were included as separate variables. The excess risk for carcinomas of the paranasal sinuses and mastoid process was associated with internally deposited ^{226}Ra, but probably not ^{228}Ra (Rowland *et al.*, 1978). On the other hand, in the studies of British dial painters who were exposed to lower doses (none of them engaged in brush pointing), no bone sarcomas were observed (Baverstock & Papworth, 1985).

No further updates of bone cancer among radium watch-dial painters have been published

in recent years, but new analyses using data from the US studies have appeared. Bijwaard *et al.* (2004) developed two-mutation mechanistic models fitting animal and human data on bone cancer. They reported that the results using data for watch-dial painters agree well with those for studies of radium-exposed beagles. The best fit for the watch-dial painters had equal cell killing terms in both mutation rates, but a nearly equally well-fitting model could be constructed with cell killing only in the second mutation rate, as in the analysis of beagle data. In an analysis of data on bone and sinus cancers for radium watch-dial painters using a two-mutation model, Leenhouts & Brugmans (2000) reported that the model parameters from the best fit were consistent with cellular radiobiological data. The fitted dose–response relationships were linear–quadratic with radium intake and with α-particle radiation dose, and did not support a model involving a threshold dose. The risks at low doses were estimated to be about a factor of 10 lower than those based on a linear extrapolation from high doses.

Bone sarcomas were the major late effect among patients with tuberculosis, ankylosing spondylitis, and other diseases who were treated with high doses of ^{224}Ra (mean bone surface dose, 30 Gy) in a cohort study in Germany (Nekolla *et al.* 2000; see Table 2.8 on-line). Nekolla *et al.* (2000) used an improved dosimetry system – relative to previous analyses in that cohort – with modified doses to the bone surface, particularly for exposures at younger ages. Virtually all of the tumours in the cohort could be attributed to exposure to radium, reflecting the very high bone-surface doses received. In contrast to previous analyses of this cohort, the excess absolute risk (EAR) decreased with increasing age at exposure. As before, the EAR for a given total dose decreased with increasing duration of exposure; however, there was little evidence of such an effect at the lower doses received by this cohort, which was suggested to be in agreement with microdosimetric considerations and general radiobiological experience (Nekolla *et al.*, 2000). Among ankylosing spondylitis patients treated with lower doses of ^{224}Ra (mean bone-surface dose, 5 Gy) in another German cohort, there was an excess of bone cancer relative to population rates, but based on only four cases (Wick *et al.*, 1999).

A case–control study of osteosarcoma in Wisconsin (USA) looked for any correlation with estimated levels of total α-particle activity and levels of ^{226}Ra and ^{228}Ra in drinking-water, by linking measurements to Zone Improvement Plan (ZIP) codes (Guse *et al.*, 2002; see Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.9.pdf). No evidence of an association was found. However, the study lacked individual exposure data, other than ZIP code. In addition, the exposures were much lower than those for the ^{226}Ra watch-dial painters.

(b) *Leukaemia*

Wick *et al.* (2008) and Nekolla *et al.* (1999, 2000) reported findings for leukaemia in two separate cohorts of ankylosing spondylitis patients in Germany (see Table 2.8 on-line). Exposures from ^{224}Ra in the former cohort were lower than those in the latter cohort. Wick *et al.* (2008) found a significantly raised risk of leukaemia – particularly myeloid leukaemia – relative to population rates, which was in line with experimental findings from mice injected with varying amounts of this radionuclide. Nekolla *et al.* (1999) reported eight leukaemia cases in their cohort, compared with 3.8 expected from population rates (P = 0.04). When a 2-year lag was used, the corresponding P value was 0.08. [The Working Group noted that although there were indications of raised leukaemia risks in both of the ^{224}Ra cohorts, these findings were based on small numbers of cases and that dose–response analyses were not performed.]

No excess incidence of leukaemia was observed among watch-dial painters or among watch-dial

painters with measured body burdens in the USA (Spiers *et al.*, 1983). However, leukaemia occurred early in female watch-dial painters and an excess of leukaemia was observed among male watch-dial painters (Stebbings, 1998).

(c) Other cancers

Little information has appeared since the previous *IARC Monograph* (IARC, 2001) on the association between exposure to radium and risk of cancers other than bone cancer and leukaemia. In particular, there are no new findings for the radium watch-dial painters nor from the ^{224}Ra medically exposed cohorts. The excess risk for carcinomas of the paranasal sinuses and mastoid process seen among US radium watch-dial painters was associated with internally deposited ^{226}Ra, but probably not ^{228}Ra (Rowland *et al.*, 1978). In particular, these cancers occurred mainly among subjects exposed to ^{226}Ra only, and infrequently among those exposed to both ^{226}Ra and ^{228}Ra (Rowland *et al.*, 1978). High ^{222}Ra levels were found in the mastoid cavity of subjects whose body burdens were primarily from ^{226}Ra, and suggested that radioactive decay of ^{222}Ra released into this cavity by decay of ^{226}Ra in the surrounding bone is the cause of these cancers (Evans, 1966).

In a cohort of USA radium watch-dial painters, suggestive positive associations were observed between estimated radium body burden and lung cancer and multiple myeloma. These cancers, particularly multiple myeloma, were more closely associated with duration of employment than with radium intake (Stebbings *et al.*, 1984). [The Working Group noted that duration of employment corresponded to duration of γ-radiation exposure, and was a surrogate for cumulative external γ-radiation dose.] No increased risk of lung cancer was observed in cohorts of patients injected with ^{224}Ra (Nekolla *et al.*, 1999; Wick *et al.*, 1999).

Stebbings *et al.* (1984) also reported an association between estimated radium burden and mortality from breast cancer in US radium watch-dial painters. This association may have been confounded; in particular, 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. A raised risk of breast cancer was also observed in a cohort of women in the United Kingdom who worked with radium paint (one sided $P = 0.077$) (Baverstock *et al.*, 1981). Due to small body burden of radium compared to the US luminizers, no further analyses were performed with regard to α-particles. In analyses stratified for both age at start of luminizing (< 30 versus ≥ 30 years) and γ-radiation dose (< 0.2 versus ≥ 0.2 Gy), the excess risk was seen to be predominant among the younger age group receiving ≥ 0.2 Gy of γ-radiation (one-sided $P = 0.009$). Nekolla *et al.* (1999) reported a significantly raised risk of breast cancer among patients injected with ^{224}Ra. Such an association was not observed among patients injected with low-dose ^{224}Ra (Wick *et al.*, 1999). [The Working Group noted indications of a raised breast cancer risk in an unexposed group in the analysis conducted by Nekolla *et al.* (1999), suggesting that factors other than radiation may have contributed to the breast cancer excess seen in the exposed group].

Statistically significant increases in risk of soft-tissue sarcomas, kidney cancer, urinary bladder cancer, liver cancer and thyroid carcinoma were also reported among patients injected with high doses of ^{224}Ra (Nekolla *et al.*, 1999), but not among those who received low doses (Wick *et al.*, 1999). [The Working Group noted that although significant increases for the aforementioned types of cancer were reported by Nekolla *et al.* (1999) relative to population rates (Table 2.8 on-line), the corresponding data for a control group of unexposed patients were not presented. For the other ^{224}Ra cohort, Wick *et al.* (1999) presented results for both exposed and unexposed patients (Table 2.8 on-line). However,

in both cohorts, the numbers of cases of specific cancer types were generally small.]

In Thailand, a case–control study of cancers of the upper digestive tract reported a statistically significant association with intakes of radium in drinking-water, based on small numbers of cases (Hirunwatthanakul *et al.*, 2006; Table 2.9 on-line). [The Working Group noted that in contrast to the other study on radium in drinking-water (Guse *et al.*, 2002), this study collected information on individuals' daily consumption of drinking-water and on other potential risk factors, although for the cancer cases (but not the controls) this information was provided mainly by relatives.]

(d) Synthesis

As discussed previously by IARC (2001), the studies of cancer risk among US radium watch-dial painters showed consistent increases in the risk for bone sarcoma related to exposure to α-particles, and both ^{226}Ra and ^{228}Ra contributed significantly and independently to this elevated risk. The previous Working Group (IARC, 2001) associated the excess risk for carcinomas of the paranasal sinuses and mastoid process in this cohort to internally deposited ^{226}Ra, but probably not ^{228}Ra. No further data was available to the Working Group that altered the conclusions in the previous *IARC Monograph*.

The most recent analysis of the risk of bone tumours among patients treated with ^{224}Ra for tuberculosis or ankylosing spondylitis supports the strong association observed by the previous Working Group (IARC, 2001).

There is some evidence of elevated leukaemia risks in the two cohorts of patients injected with ^{224}Ra cohorts. However, these findings were based on small numbers of cases, and dose–response analyses were not performed. No excess incidence of leukaemia was observed among US radium watch-dial painters overall. The possibility that radium isotopes increase leukaemia risk in humans cannot be ruled out, but the available evidence did not permit any causal relationship to be established.

2.2.2 Mixed α-particle emitters

(a) Thorium-232

The previous IARC evaluation of ^{232}Th and its decay products, administered intravenously as a colloidal dispersion of ^{232}Th dioxide, was based on increased risk of primary liver cancer, including haemangiosarcomas, and leukaemia, excluding chronic lymphocytic leukaemia (IARC, 2001).

The evidence of cancer risk associated with Thorotrast (stabilized ^{232}Th dioxide) exposures came mainly from cohort studies in Denmark, Germany, Japan, Portugal, and Sweden (IARC, 2001). Thorotrast was used extensively in medical practice between the 1930s and the 1950s as a radiographic contrast agent. Owing to its colloidal nature, Thorotrast is retained mostly in the reticuloendothelial system (liver, spleen, and bone marrow) after intravenous injection.

(b) Liver and biliary tract cancers

Cohort studies in Denmark, Germany, Japan, Portugal, Sweden, and the USA demonstrated significantly increased risks for liver cancer (approximately one-third being haemangiosarcomas), which were significantly correlated with the volume of Thorotrast injected. The incidence of and mortality from liver cirrhosis were also significantly increased in all studies in which liver cirrhosis was an end-point (Mori *et al.*, 1999; dos Santos Silva *et al.*, 2003). A combined analysis of the cohorts of Danish and Swedish Thorotrast patients (Travis *et al.*, 2003) showed statistically significant trends with a surrogate measure for cumulative radiation dose in the incidence of primary liver cancer and cancer of the gallbladder. [The Working Group noted that key strengths of this analysis were the long-term follow-up, the availability of cancer incidence data, the large number of cases observed and the opportunity to conduct a dose–response

analysis, albeit based on a surrogate measure.] Among patients injected with 20 mL or more of Thorotrast, the cumulative excess cancer incidence remained elevated for up to 50 years, and approached 97%. Analysis of a smaller cohort of Thorotrast patients in the USA, based on mortality data, yielded comparable findings (Travis *et al.*, 2003). An extended mortality follow-up of Thorotrast patients in Portugal (dos Santos Silva *et al.*, 2003) showed statistically significant trends with a surrogate measure for cumulative radiation dose for all cancers combined, and for the grouping of liver cancer and chronic liver diseases. Becker *et al.* (2008) described an extended follow-up of mortality in the German Thorotrast cohort, which is the largest single study of Thorotrast patients. By the end of 2004, nearly all of these patients had died. For all malignant neoplasms and for cancers of the liver and intrahepatic bile ducts, both the SMR and the relative risk compared to a control group increased with increasing time since first exposure. An earlier analysis of the German cohort (van Kaick *et al.*, 1999) reported associations between the amount of Thorotrast injected and mortality from cancers of the liver, gallbladder and extrahepatic bile ducts. A Japanese cohort (Mori *et al.*, 1999) also showed increased mortality from liver cancer among Thorotrast patients. In this publication, the risk associated with increasing time since first exposure was also reported, but no formal statistical test for trend was presented (see Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.10.pdf).

Results of the continued follow-ups of Thorotrast exposed patients are summarized in Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.11.pdf.

(c) Haematological malignancies

A significantly increased risk of leukaemia excluding chronic lymphocytic leukaemia has been reported in the Thorotrast cohorts in Denmark, Germany, Japan, Portugal, Sweden, and the USA. A combined analysis of the cohorts of Danish and Swedish Thorotrast patients (Travis *et al.*, 2003) in which the incidence of leukaemias (excluding chronic lymphocytic leukaemia) was significantly higher than that among unexposed patients showed no statistically significant trend in incidence associated with this dose measure. Analysis of a smaller cohort of Thorotrast patients in the USA, based on mortality data, yielded comparable findings (Travis *et al.*, 2001). In an extended mortality follow-up of Thorotrast patients in Portugal (dos Santos Silva *et al.*, 2003), mortality from benign and malignant haematological diseases and from leukaemia (excluding chronic lymphocytic leukaemia) remained high relative to national rates over the follow-up period (more than 40 years after administration of Thorotrast), but did not show a trend with the surrogate dose measure. In an extended follow-up of mortality in the German Thorotrast cohort (Becker *et al.* (2008), statistically significantly elevated risks were seen for malignancies of the haematopoietic system (particularly myeloid leukaemia). An earlier analysis of the German cohort (van Kaick *et al.*, 1999) reported associations between the amount of Thorotrast injected and mortality from a grouping of myeloid leukaemia and myelodysplastic syndrome (see Table 2.10 on-line).

(d) Other cancers

Increased risks for cancers at other sites were reported in some studies but not consistently. A combined analysis of the cohorts of Danish and Swedish Thorotrast patients (Travis *et al.*, 2003) showed statistically significant trends with a surrogate measure for cumulative radiation dose in the incidence of cancers of the pancreas,

peritoneum and other digestive organs. [The Working Group noted that the excess risks for site-specific cancers should be interpreted with caution because of the potential bias associated with the selection of cohort participants, non-comparability of the internal and external comparison groups, and confounding by indication.] In an extended follow-up of mortality in the German Thorotrast cohort (Becker *et al.*, 2008), statistically significantly elevated risks were seen for cancer of the pancreas, brain, and prostate. The earlier analysis of the German cohort by van Kaick *et al.* (1999) did not find a raised risk for cancer of the prostate, but this analysis (unlike the most recent analysis by Becker *et al.*, 2008) did not take into account the different age distributions of the exposed and unexposed groups (See Table 2.10 on-line).

The Thorotrast studies give mixed results on lung cancer risk (See Table 2.11 on-line), although patients given Thorotrast exhale high concentrations of ^{220}Rn (thoron). [The Working Group noted that the interpretation of these findings is hampered by the lack of information on smoking.] Studies in the USA and China of workers exposed to thorium by inhalation of fine particles containing thorium and its decay products reported a raised risk of lung cancer relative to national rates and – in an updated analysis of miners in China (Chen *et al.*, 2003) – relative to an unexposed control group (see Table 2.10 on-line). However, this latter study did not incorporate a dose–response analysis. Furthermore, the presence in the Chinese mines of silica dioxide and rare-earth elements raises concerns about possible confounding. The other occupational study – of thorium workers in the USA – did not show an association between lung cancer and potential for thorium exposure (Liu *et al.*, 1992; Table 2.10 on-line). Furthermore, data on smoking were not available for either of these occupational studies.

(e) Synthesis

Results of the continued follow-up studies of patients exposed to Thorotrast continue to show raised risks several decades after first exposure for all malignant neoplasms combined, with consistently large relative risks seen for liver cancer and malignancies of the haematopoietic system. The risk of liver cancer increased with increasing values for a surrogate of radiation dose in analyses of the Danish/Swedish, German, Portuguese, and US cohorts.

An earlier analysis of the German cohort reported an association between a measure of radiation dose and mortality from myeloid leukaemia and myelodysplastic syndrome. In contrast, analyses of the grouping of haematopoietic malignancies in the Danish/Swedish, Portuguese and US cohorts did not show an association with a surrogate of dose; however, these analyses were not conducted specifically for leukaemia other than chronic lymphocytic leukaemia in the Portuguese and US cohorts.

Large increased risks of cancers of the extrahepatic bile ducts and of the gallbladder were reported in the two largest analyses of Thorotrast patients (Table 2.11 on-line). In view of their integral relationship to the liver, in which most of the injected Thorotrast is deposited, the extrahepatic bile ducts are likely to receive substantial α-particle exposure. Although the gallbladder is a minor site of Thorotrast storage, its location on the visceral surface of the liver may lead to continual α-particle exposure.

Pancreatic cancer risk is elevated in the German and Danish/Swedish Thorotrast cohorts, although the relative risks tend to be lower than those for the aforementioned cancer sites (Table 2.11 on-line). In the latter cohort, there is also borderline evidence of an association with a surrogate measure of radiation dose. Doses to the pancreas are likely to be notably lower than these to the liver or spleen, although the anatomical juxtaposition of a portion of the pancreas to the

spleen may have led to higher doses. However, information on smoking habits is lacking in these studies. Prostate cancer is also significantly elevated in the German and Danish/Swedish Thorotrast cohorts (Table 2.11 on-line), although there has been no analysis of prostate cancer risk in relation to the amount of Thorotrast injected or any other measure of radiation exposure. Doses to the prostate are likely to be small relative to those for organs such as the liver.

Raised risks have also been reported among Thorotrast patients for several other types of cancer, although the interpretation of these findings is unclear largely because of possible confounding by factors that led to the exposure. This is particularly important for brain cancer because many of these patients were examined with Thorotrast for cerebral angiography.

Studies of workers exposed to thorium by inhalation of fine particles containing thorium and its decay products, together with some – but not all –studies of Thorotrast patients have reported raised risks of lung cancer. However, possible differences in smoking habits, and – among miners – possible confounding by other exposures must also be considered.

Overall, large, statistically significant relative risks between exposure to Thorotrast and primary liver cancer, leukaemia (excluding chronic lymphocytic leukaemia), cancers of the extrahepatic bile ducts, and cancer of the gallbladder have been observed in the two largest analyses and, in several instances, show associations with measures of exposure. For pancreatic and prostate cancers, significantly raised risks were observed in the two largest analyses but these risks are lower than those for aforementioned cancer types and confounding cannot be excluded. No substantive new evidence on cancer risks following inhalation of ^{232}Th has appeared since the publication of the previous *IARC Monograph* (IARC, 2001).

2.2.3 Plutonium

The previous IARC evaluation of plutonium was based on an increased risk of lung cancer, liver cancer and bone sarcoma. That Working Group noted that human exposure to ^{239}Pu could also include exposure to ^{240}Pu (IARC, 2001).

Plutonium is an element used mostly for nuclear weapons production, and the production of mixed oxide fuels. Most of the exposure to plutonium is among workers involved in chemical or mechanical processing of plutonium and in nuclear weapons or nuclear power production. Several large groups of workers exposed to plutonium have been studied in the USA, United Kingdom, and the Russian Federation. Exposures have occurred since the 1940s when weapons-grade plutonium production was started in those countries. Several accidents also exposed people not working in the above industries to plutonium.

The major exposure pathways to plutonium are inhalation and, to a much lesser extent, wounds (the latter takes place mostly in workers). Only a small percentage of plutonium entering the gut is absorbed into blood, and consequently ingestion is not usually a major exposure pathway. After inhalation intake, plutonium is redistributed in the body, and is retained mostly in lung, liver and bone, which receive the largest doses from incorporated plutonium.

The previous IARC evaluation was primarily based on a cohort of workers employed at the Mayak plant in the Russian Federation, where exposure to plutonium (mostly ^{239}Pu) was substantial. Dose–response relationships were demonstrated for cancers of the lung, liver and bone in both men and women exposed to a broad range of doses. Cancers at other sites were not studied at the time. The results of the most informative studies from the previous *IARC Monograph* and of newer studies are summarized in Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.12.pdf

and Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.13.pdf.

(a) Cancer of the lung

In a recent analysis of data from Hanford plant, USA, potential for exposure to plutonium was classified in three groups (minimal, non-routine or limited, and routine potential) using a job-exposure matrix (Wing *et al.*, 2004). Mortality rates for non-external causes of death, all cancers, plutonium-related cancers (lung, liver, bone and connective tissue, and lymphatic tissue cancers), and some other cancers were lower in workers with potential routine or non-routine exposure to plutonium than in other Hanford workers [probably due to healthy worker effect]. However, mortality from all cancers, plutonium-related cancers, and lung cancer was associated with duration of employment in jobs with routine potential for plutonium exposure.

Lung cancer mortality among workers at the Rocky Flats plant was analysed in a nested case–control study by Brown *et al.* (2004) and Brown & Ruttenber (2005); Table 2.13 on-line). Lung doses from incorporated plutonium were assessed by a model based on Publication 30 of the International Commission on Radiological Protection (ICRP, 1979). External dosimetry data were extracted from computerized records of individual workers. Exposure levels ranged up to hundreds mSv of plutonium lung dose and tens of mSv of external dose. Using dose estimates to the lung epithelium, a statistically significant risk of lung cancer was found when plutonium exposure was characterized in terms of the dose of α-particles to the lung epithelium. [The Working Group noted that this study did not include adjustment for smoking as the authors reported that the odds ratios were not changed by more than 10%. Later, Brown & Ruttenber (2005) stated that smoking was not confounding the relationship between the dose of α-particles to the lung and the risk from lung cancer mortality.]

Several analyses of lung cancer mortality among Mayak workers have been published; a series of earlier publications were reviewed in the previous *IARC Monograph* (IARC, 2001). The analyses by Kreisheimer *et al.* (2000) were restricted to reactor workers (assumed to have zero plutonium lung dose), and radiochemical or plutonium workers with estimates of plutonium body burden and lung dose. Analyses were conducted within the cohort, rather than through comparisons with Russian population rates. Lung cancer mortality was associated with lung dose from plutonium, but not external dose. [The Working Group noted that no adjustment was made for smoking in this analysis]. In an extended follow-up, using new dosimetry data and smoking information, Kreisheimer *et al.* (2003) analysed lung cancer mortality among men in the same cohort. External dose was not associated with lung cancer mortality in this study whereas a highly significant dose–response association was seen for plutonium lung dose. There was no departure from linearity for the effect of plutonium.

The above study (Kreisheimer *et al.*, 2003) was restricted to workers monitored for plutonium and only from the time they were monitored. To allow for better analyses of external dose–response relationship for the workers who were not monitored, a surrogate characteristic of potential exposure to plutonium was developed based on detailed occupational history data of Mayak workers (Khokhryakov *et al.*, 2000; Krahenbuhl *et al.*, 2005), and was used in analyses published by Shilnikova *et al.* (2003), Gilbert *et al.* (2004), and Sokolnikov *et al.* (2008). A significant dose-related increase in lung cancer risk was demonstrated by Gilbert *et al.* (2004). The ERR of lung cancer at age 60 in women was 4 times higher than in men, reflecting very different background lung cancer rates in men and women. No departure from linearity was found for plutonium lung dose and lung cancer. For the subcohort of workers hired during 1948–58, analyses

were repeated restricting the cohort to those monitored for plutonium, reactor and auxiliary workers, and to those who also had available smoking status (as a yes/no variable) information (Gilbert *et al.*, 2004). Following adjustment for smoking, the ERR/Gy for internal dose was changed only slightly in both men and women and the women/men ratio of the ERR/Gy was not greatly modified. The analysis of Sokolnikov *et al.* (2008) was restricted to workers with at least 5 years of follow-up. Smoking data were available for the full cohort. A surrogate measure of potential to plutonium exposure was used for workers not monitored for plutonium (or until they were monitored). A significantly increased smoking-adjusted risk of lung cancer was found in workers with total accumulated plutonium lung dose in the range of 0.2–0.3 Gy and above. There was no departure from linearity. Smoking habits in the cohort of Mayak workers showed striking differences between genders, with 75% of men and only 4.2% of women reporting smoking.

The association between lung cancer risk and exposure to plutonium among Mayak workers was also demonstrated in other analyses (Jacob *et al.*, 2005; Jacob *et al.*, 2007).

(b) Cancer of the liver and bone

Initially, in a cohort of early Mayak workers who received largest doses of both external and plutonium exposures, the analyses of bone and liver cancer mortality were done using plutonium body-burden levels (Gilbert *et al.*, 2000; Koshurnikova *et al.*, 2000). All analyses were stratified by age, calendar year, and gender, and adjusted for external dose. Among bone and soft-tissue cancers, included were only those that developed in sites directly adjacent to the bone where plutonium exposure could take place. Bone cancer mortality was significantly increased in workers with extremely high plutonium body–burden levels. The same was true for liver cancer mortality, although liver cancer risks in men and women differed substantially (Gilbert *et al.*, 2000) [The Working Group noted that this was probably due in part to gender differences in background mortality (mostly related to different alcohol habits)]. Of 60 liver cancers identified in this subcohort, 10 were haemangiosarcomas, which are liver tumours found among subjects exposed to extremely high levels of α-particles (such as exposed to Thorotrast) [The Working Group noted that plutonium workers are currently not known to be exposed to vinyl chloride, a chemical which is strongly associated with liver haemangiosarcoma (IARC, 2008)]. One of limitations of the Mayak workers' cohort is the incomplete coverage of plutonium monitoring. However, among plutonium workers that were not monitored for internal exposure, the risk of death from bone and liver cancer was significantly higher compared to reference population.

A follow-up analysis using improved dosimetry conducted in 2008 focusing on absorbed dose to the bone and liver, rather than body burden, confirmed the original results (Sokolnikov *et al.*, 2008). Although bone and liver cancer among Mayak workers are indicative for plutonium effects, the small number of cases results in some uncertainty about the shape of the dose–response relationship for these tumour sites.

(c) Other cancers

McGeoghegan *et al.* (2003) analysed mortality and cancer morbidity of female workers employed at British Nuclear Fuels Limited (BNFL) and the Atomic Energy Agency, in the United Kingdom. The overall and the majority of site-specific SMRs for radiation workers other than plutonium workers were lower when compared to the population of England and Wales; SMRs for all causes and all malignant cancers were significantly lower. On the other hand, compared to other radiation workers, mortality from all causes, all malignant cancers and breast cancer in plutonium workers were significantly higher. The ratio of SMR in plutonium workers to other radiation workers was 2.20 for all causes ($P < 0.01$), 3.30

for all malignant cancers ($P < 0.01$), and 3.77 for breast cancer ($P < 0.05$).

Analyses of Mayak workers published by Shilnikova *et al.* (2003) demonstrated a statistically significant increased risk of solid cancers other than lung, liver and bone in relation to systemic body burden (i.e. whole body excluding lung). [The Working Group noted that it was unlikely that exposure to other carcinogens could account for these findings.] However, the absence of organ-specific doses precluded analyses on specific solid cancers. There was no significant risk of leukaemia related to exposure to plutonium; the point estimate for the plutonium body burden dose–response with regard to leukaemia death was negative but not statistically significant ($P > 0.5$).

(d) Synthesis

Analyses of cancer risk following exposure to plutonium in Mayak workers show evidence of plutonium carcinogenicity primarily in lung, liver and bone, the organs in which high doses of incorporated plutonium are accumulated. Risks were seen to increase in a dose-dependent manner. Recent analyses demonstrated that increased lung cancer risks remained after adjustment for tobacco smoking.

Analyses of Mayak workers also demonstrated an increased risk of solid tumours other than lung, liver and bone in relation to exposure to plutonium. However, site-specific analyses were not conducted. Little information was available on the association between exposure to plutonium and leukaemia.

2.2.4 Uranium

All isotopes of uranium are radioactive. Naturally occurring uranium consists of a mixture of three radiactive isotopes: ^{234}U (0.005%), ^{235}U (0.711%), and ^{238}U (99.284%) (IAEA, 2004). ^{234}U is a pure α-particle emitter, and ^{235}U and ^{238}U are mixed α-particle emitters with other emissions of β-particles and γ-radiation. Therefore, external exposure to natural or depleted uranium, and internal deposition of uranium, implies exposure to α- and β-particles and γ-radiation (Bleise *et al.*, 2003). In some settings, bremsstrahlung radiation (photons) is also present due to the interaction of β-particles from uranium decay with dense material. Uranium may also have chemical toxicity effects. Due to the very long half-life of its main isotope (^{238}U; 4.5 x 10^9 years), natural uranium is considered a low specific radioactive element. Epidemiological research on the health effects of exposure to natural and depleted uranium is made difficult by the typically low dose rates associated with such exposures.

Occupational exposure to natural uranium happens in the civil nuclear industry and the atomic weapons industry especially from the mining and processing of uranium ores (insoluble oxides) or as exposure to "yellowcake," the soluble form of the oxide (UO_4), in the chemical purification of uranium. Natural uranium may also be a component of drinking-water (Kurttio *et al.*, 2002). Uranium millers and individuals involved in other uranium-processing operation may be exposed to α- and β-particles from inhaled or ingested uranium dust. Inhalation of insoluble uranium particles is the major pathway of exposure for the lung (IARC, 2001). Inhaled or ingested soluble uranium that becomes systemic may have more chemotoxicity than radiotoxicity. The use of depleted uranium munitions, including enforced armour-piercing projectiles and tank armour, may increase the exposure of certain populations to uranium. The oxide dust produced by the impact of the elemental munition on hard targets has a soluble component. The impact also releases insoluble uranium metal from fragments (Bleise *et al.*, 2003).

Of four studies that were considered in the previous *IARC Monograph* (Polednak & Frome, 1981; Dupree *et al.*, 1987; Checkoway *et al.*, 1988; Ritz, 1999), all of which were occupational cohorts, updated results were later published

for two larger studies. This section reviews the epidemiological literature published since the previous *IARC Monograph*. Given the radiological properties of uranium, it should be noted that the independent carcinogenic effects of exposure to γ-radiation, β-particle radiation, and α-particle radiation are covered in separate sections of this volume. This review of the epidemiological literature focuses on studies of worker populations in which large numbers of people were exposed to relatively high levels of uranium as a consequence of milling, enrichment, or fabrication processes, and studies of populations that were exposed to depleted uranium. Studies of uranium miners are excluded from this review because their exposure is primarily to radon (and radon daughters) which are covered in a separate section of this *Monograph*, and not repeated here. Similarly, workers in the nuclear power industry and weapons industry who worked in settings where uranium exposures contribute a small amount to the collective dose are excluded from this review because their exposure was primarily to radiological hazards (e.g. external exposure to γ-radiation or internal exposure to plutonium), which are covered in separate sections of this *Monograph*, and not repeated here.

(a) Occupational studies

Interpretations of occupational cohort analyses based upon external comparisons, in which mortality in a worker population is compared to mortality in an referent population by calculation of SMRs, are complicated by potential bias due to health-related selection into employment (sometimes referred to as the healthy worker hire effect). In addition, SMR analyses are often conducted in settings in which the investigator lacks quantitative exposure estimates. Such analyses may combine together a small subgroup of workers with substantial potential for uranium exposure with a larger group of people who had little or no uranium exposure; consequently, these studies often have limited ability to detect the potential adverse effects of uranium exposures. Where available, this review gives greater attention to occupational cohort analyses that are based upon internal comparisons, in which workers' exposures were quantified permitting comparisons between worker groups with different exposure histories. However, quantifications of internal and external radiation doses from uranium in occupational cohort studies are often accompanied with substantial uncertainty. Therefore, the interpretation of study results based upon contrasts drawn between workers with different levels of uranium exposure may be complicated by bias to errors in exposure estimation (see Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-04-Table2.14.pdf).

External exposure to penetrating forms of ionizing radiation may result in whole-body irradiation. In contrast, examination of the effects of internal exposure to uranium typically focuses on the organ systems through which uranium particles pass. Inhalation is a primary route of exposure to uranium in many occupational settings, leading to interest in lung cancer and cancers of the upper aerodigestive tract. Urinary tract and haemato- and lymphopoietic cancers have also been of interest because insoluble uranium may deposit in nodes, and soluble uranium compounds are transported by the blood to the kidney for excretion.

(i) Uranium millers

Three cohort studies of US uranium millers have been reported since the previous *IARC Monograph*; all report on the analysis of SMRs. [The Working Group noted that it is likely that two of the studies (Boice *et al.*, 2007, 2008) were partly included in the pooled analyses by Pinkerton *et al.* (2004). Due to different follow-up periods for those studies, it was impossible to quantify the exact extent of overlap.] Although in all three cohort studies mortality from all causes was less than expected (based upon comparisons

to US mortality rates), in two of the three studies, a non-significant excess of lung cancer mortality was reported (Pinkerton *et al.*, 2004; Boice *et al.*, 2007), as well as excesses of lymphatic and haematopoietic cancers other than leukaemia in the largest of the cohort studies (Pinkerton *et al.*, 2004). In that study, which was a pooled study of seven uranium miller cohorts, a significant excess of lung cancer mortality was observed in analyses using state mortality rates as a comparison (SMR, 1.51; 95%CI: 1.19–1.89). Potential confounding by smoking, silica exposure, or other occupational hazards complicated the interpretation of these results, and these studies lacked a direct measure of cumulative exposure to uranium.

(ii) Uranium enrichment and fabrication workers

Since the previous *IARC Monograph*, three studies have been reported on mortality among workers at US uranium enrichment and fabrication plants (see Table 2.14 on-line). The Mallinckrodt Chemical Works at St. Louis, Missouri, processed tonnage quantities of uranium ore into pure uranium tetrafluoride and metal. Dupree-Ellis *et al.* (2000) estimated the effects of external radiation on cancer mortality among workers at this facility. All-cause mortality was significantly lower than expected based upon national rates (SMR, 0.90; 95%CI: 0.85–0.96), and SMRs were 1.05 (95%CI: 0.93–1.17) for all cancers, and 1.17 (95%CI: 0.54–2.18) for kidney cancer mortality. There was a positive dose–response relationship between kidney cancer and external radiation; the ERR/Sv for kidney cancer was 10.5 (90%CI: 0.6–57.4). Seven men who died of kidney cancer had worked in the pitchblende processing area, where external radiation exposure was potentially high because most operations were done manually.

The US Department of Energy's Y-12 facility, located in Oak Ridge, Tennessee, operated as a uranium enrichment facility, and later as a facility for fabrication of nuclear weapons parts, and recycling and recovery of uranium and other radioactive materials. A study of Y-12 workers examined associations between external and internal radiation dose and lung cancer mortality (Richardson & Wing, 2006). Internal exposure to ionizing radiation was primarily in the form of α-particle radiation from uranium isotopes, with the primary route of exposure being inhalation of uranium dust. Cumulative external radiation dose (under a 5-year lag) was positively associated with lung cancer mortality; cumulative internal radiation dose exhibited little evidence of association with lung cancer mortality.

The US Department of Energy's Portsmouth Gaseous Diffusion facility, located in Piketon, Ohio, operated as a uranium enrichment facility. A nested case–control analysis was conducted to examine associations between mortality from several cancers, including lung cancer, and external dose; no significant association was observed (Ahrenholz *et al.*, 2001).

Two studies have been reported on mortality among workers at fuel fabrication and uranium production facilities in the United Kingdom (see Table 2.14 on-line). McGeoghegan & Binks (2000b) reported on the association between external radiation dose and mortality among workers employed at the Springfields Uranium Production Facility. No estimates of internal exposure to uranium were used in this study. [The Working Group noted that with respect to incidence, a positive association between all cancers (including or excluding leukaemias) and cumulative external radiation dose under a 20-year lag was observed; this was largely due to the positive association between cumulative external radiation dose and incidence of lung cancer (trend statistic, 1.72; $P < 0.05$) and all lymphatic and haemopoetic cancers (trend statistic, 2.30; $P < 0.05$).] A follow-up study of a cohort of workers at the Capenhurst plant (the primary activity of which was enrichment of uranium) was also carried out, (McGeoghegan

& Binks, 2000a). A positive association was observed between bladder cancer incidence and cumulative external radiation exposure under a 20-year lag (trend statistic, 1.95; $P = 0.035$).

Baysson *et al.* (2000) reported on mortality among 356 workers employed in the metallurgy department of the French Atomic Energy Commissariat. Job and hazard forms were used to derive qualitative hazard assessments for 30 products. The risk of all-cancer mortality appeared to increase with increasing duration of exposure to radionuclides and chemical; given the small numbers of events, dose–response associations were not estimated for other outcomes.

(iii) Depleted uranium

During the manufacture of nuclear fuel for most types of reactors, the relative concentration of isotopes with higher radioactivity is increased. A by-product of this enrichment process is depleted uranium. Consequently, depleted uranium is constituted of the same three isotopes as natural uranium, but with lower relative concentrations of ^{235}U and ^{234}U. Radiotoxicity of natural uranium is 60% higher than that of depleted uranium, while their chemotoxicity is similar (Bleise *et al.*, 2003).

Cohort studies of Swedish and Danish soldiers deployed to the Balkans have been reported (Gustavsson *et al.*, 2004; Storm *et al.*, 2006) with follow-up for cancer incidence. Most persons were deployed for short periods (e.g. 6 months), and no uranium exposures were quantified (see Table 2.14 on-line). Among soldiers in the Swedish cohort (Gustavsson *et al.*, 2004), cancer incidence was slightly higher than expected (SIR, 1.2; 95%CI: 0.9–1.7). There was no excess of lung cancer (one case observed versus 0.8 expected in men, and one case observed versus 0.1 expected in women), but there were eight cases of testicular cancer versus 4.6 expected (SIR, 1.9; 95%CI: 0.8–3.7). Among Danish soldiers deployed to the Balkans (Storm *et al.*, 2006), cancer incidence was slightly lower than expected among male soldiers (SIR, 0.9; 95%CI: 0.7–1.1, based on 84 cases) and slightly higher than expected among female soldiers (SIR, 1.7; 95%CI: 0.9–3.0, based on 12 cases). Bone cancers were in excess among men (SIR, 6.0; 95%CI: 1.6–15.3, based on four cases).

Kang & Bullman (2001) reported results from a follow-up study on mortality of a cohort of 621902 US Gulf War veterans who arrived in the Persian Gulf before May 1, 1991, and a cohort of 746248 US non-Gulf veterans. Follow-up for mortality was conducted through 1997. Male Gulf War veterans had a slightly lower all-cause mortality rate than non-Gulf veterans (RR, 0.95; 95%CI: 0.92–0.99), and female Gulf War veterans had a slightly higher all-cause mortality rate than non-Gulf veterans (RR, 1.16; 95%CI: 0.97–1.38). Male Gulf War veterans also had a slightly lower all-cancer mortality rate than non-Gulf veterans (RR, 0.90; 95%CI: 0.81–1.01), and female Gulf War veterans had a slightly higher all-cancer mortality rate than non-Gulf veterans (RR, 1.11; 95%CI: 0.78–1.57). A potential limitation of the study was that some of the non-Gulf War veterans may have been less healthy than the veterans sent to the Persian Gulf.

Macfarlane *et al.* (2003) examined cancer incidence rates in a cohort of 51721 United Kingdom Gulf war veterans and 50755 service personnel matched for age, sex, rank, service, and level of fitness who were not deployed in the Gulf. Cancer incidence was ascertained over the period up from 1 April 1991 (the end of the Gulf war) to 31 July 2002. Incidence rate ratios (IRR) were calculated comparing these two groups. There was no excess in all cancers or lung cancer among the Gulf cohort; non-significant excesses were observed for several cancer sites, including lymphoid and haematopoietic cancers (IRR, 1.30; 95%CI: 0.83–2.03), urinary tract cancers (IRR, 1.42; 95%CI: 0.61–3.32), and upper digestive tract cancers (IRR, 1.47; 95%CI: 0.53–4.14). Self-reported information was collected via surveys on exposure to potentially hazardous materials,

including depleted uranium. Among the Gulf veterans who participated in at least one of the surveys, reported exposure to depleted uranium was not associated with an excess risk of cancer overall (IRR, 0.63; 95%CI: 0.30–1.36). Macfarlane *et al.* (2005) examined cause-specific mortality in the above study. There was no overall difference in the death rates between cohorts or in malignant causes of death. Reported exposure to depleted uranium was uncommon among those deployed (7%). There was a non-significant increased risk of death among those who reported exposure (mortality rate ratio, 1.48; 95%CI: 0.83–2.64). The small proportion of Gulf Veterans who reported exposure to depleted uranium experienced a doubling in the risk of dying from non-external causes, although, again, the result was not statistically significant (mortality rate ratio, 1.99; 95%CI: 0.98–4.04). Of the nine people who reported exposure to depleted uranium and who died from a disease-related cause, seven were from cancer: three malignant cancers of the oesophagus, three malignant cancers of the brain, and one cancer of the brain of uncertain behaviour (benign/malignant).

(b) Synthesis

Uranium creates a relatively complex spectrum of radiological hazards, including external exposure to β-particles and γ-radiation, and internal exposures to α-particles, β-particles, and γ-radiation. The available epidemiological studies of the effects of internal exposure to uranium have been constrained by limitations of available historical records from routine monitoring for uranium intakes. Consistent with the evidence from studies of the distribution of uranium in humans after intakes of insoluble compounds, excesses of mortality from respiratory and lymphatic cancers have been reported in some studies of uranium millers. SMR analyses of data pooled for seven uranium miller cohorts (excluding workers known to have been employed in uranium mining) in Colorado reported excesses of lung cancer and lymphatic cancers. An excess of lung cancer mortality also was observed among the 450 uranium mill workers in the Uravan cohort. No excess of lung cancer was reported among the uranium mill workers in the Grants cohort, although excess mortality due to kidney and bladder cancer was reported in that cohort.

Several studies have quantified radiation doses among uranium-processing workers. External doses tended to be better quantified than internal doses from uranium intakes. Limitations in quantifying internal doses from uranium reflect the limitations of historical records (e.g. records were typically not available for all workers over all periods of employment), and the limitations of historical bioassay programmes for the reconstruction of internal dose estimates. Evidence of positive associations between cumulative external dose and lung cancer have been reported among workers at the Y-12 facility, and among workers at the Springfields facility, but not among workers at the Capenhurst, Mallinckrodt, or Portsmouth facilities. The magnitudes of external doses were quite low at these facilities, limiting the statistical power of such investigations. Internal doses from uranium were not associated with lung cancer mortality in analyses of the Y-12 cohort. A small study of workers employed by the French Atomic Energy Commissariat suggested an association between duration of exposure to radionuclides and all-cancer mortality.

Epidemiological studies of cancer incidence or mortality among soldiers with potential exposure to depleted uranium have used little or no quantitative assessment of exposure magnitude, which poses serious limitations in these studies of the health effects of presumably low-level exposures to uranium.

Overall, two epidemiological cohort studies of uranium enrichment workers reported significant positive associations between the radiation dose quantified by personal dosimeters and

lung cancer (McGeoghegan & Binks, 2000b; Richardson & Wing, 2006). Lung cancer risk could be caused either by external exposure to γ-radiation, or by α-particles emitted by uranium particles inhaled into the lung, or both. In addition, an excess of lung cancer mortality was observed in cohorts of mortality among uranium millers. However, these associations are not consistent across all studies, and there is the potential for confounding of these associations by smoking as well as occupational hazards other than uranium.

3. Cancer in Experimental Animals

3.1 Previous *IARC Monograph*

The carcinogenic risks to humans from internally deposited radionuclides have been reviewed by previous IARC Working Groups (IARC, 1972, 1987, 1988, 2001). Alpha-emitters have been tested for carcinogenicity at various doses and under various conditions in mice, rats, hamsters and dogs.

3.1.1 Radon-222

^{222}Rn induced respiratory tract cancers in rats (Perraud *et al.*, 1972), and lung epidermoid carcinoma, bronchioalveolar carcinoma, and nasal mucosa squamous carcinoma, in dogs by inhalation (Cross *et al.*, 1982).

3.1.2 Polonium-210

^{210}Po induced lung adenocarcinomas in hamsters by intratracheal instillation (Little *et al.*, 1978).

3.1.3 Radium-224

^{224}Ra induced osteogenic sarcomas (Luz *et al.*, 1979; Müller *et al.*, 1983) and myeloid leukaemia (Humphreys *et al.*, 1993) in mice by intraperitoneal injection. ^{224}Ra induced osteosarcomas and nasal mucosa tumours in dogs when administered by intravenous injection (Muggenburg *et al.*, 1995, 1996).

3.1.4 Radium-226

^{226}Ra induced bone sarcomas in mice by intraperitoneal injection (Taylor *et al.*, 1983), and bone sarcomas and intraocular melanomas in dogs by intravenous injection (Taylor *et al.* 1972, 1997, 2000; Lloyd *et al.* 1993, 1994a).

3.1.5 Thorium-228

^{228}Th caused osteosarcomas in dogs by intravenous injection (Mays *et al.*, 1987; Lloyd *et al.*, 1997a).

3.1.6 Thorium-230

^{230}Th in a colloidal form caused liver cancer in rats (Wesch *et al.*, 1983) and mice (Taylor *et al.*, 1993).

3.1.7 Thorium-232

^{232}Th induced hepatocellular carcinomas in hamsters by intravenous injection (Guilmette *et al.*, 1989), and liver carcinomas, intrahepatic bile-duct carcinomas and haemangiosarcomas in rats by intravenous injection (Wegener *et al.*, 1983; Wesch *et al.*, 1983).

3.1.8 Uranium

Uranium ore dust containing 44% elemental uranium induced bronchioalveolar carcinomas, bronchial carcinomas and squamous cell carcinomas in rats by inhalation (Mitchel *et al.*, 1999). An incidence of osteosarcomas (2%) was reported by Ellender *et al.* (2001) after intraperitoneal injection of uranium in mice.

3.1.9 Neptunium-237

^{237}Np induced osteosarcomas in rats when administered by intravenous injection (Sontag *et al.*, 1997), and adenocarcinomas and squamous cell carcinomas of the lung by inhalation (nose-only) exposure (Dudoignon *et al.*, 1999).

3.1.10 Plutonium-238

^{238}Pu caused lung cancer in hamsters by inhalation (Thomas & Smith, 1979), and caused lung, liver and bone cancers in dogs exposed by inhalation (Gillett *et al.*, 1988; Park *et al.*, 1997).

3.1.11 Plutonium-239

^{239}Pu caused liver, lung and bone cancers in dogs by inhalation (Dagle *et al.*, 1996; Hahn *et al.*, 1999). In mice (Taylor *et al.*, 1981; Svoboda *et al.*, 1982; Humphreys *et al.*, 1987; Oghiso *et al.*, 1994, 1997; Oghiso & Yamada, 1999), hamsters (Brooks *et al.*, 1983) and dogs (Lloyd *et al.*, 1993, 1994b) exposed to ^{239}Pu by parenteral administration, bone and liver cancers were observed; haematopoietic cancers were also observed in mice (Svoboda *et al.*, 1982).

3.1.12 Americium-241

^{241}Am induced osteoblastic osteosarcomas of the skeleton and lymphoreticular system (lymphomas and lymphosarcomas) in 314 CBA mice (Nilsson & Broomé-Karlsson, 1976) when administered by intraperitoneal injection. ^{241}Am increased the incidence of osteosarcomas in mice by intravenous injection (van den Heuvel *et al.*, 1995), and induced bile-duct adenomas and carcinomas, fibrosarcomas and haemangiosarcomas in both deer mice and grasshopper mice by intraperitoneal injection (Taylor *et al.*, 1986). Osteosarcomas were induced and one leukaemia was reported in August/Marshall hybrid rats after intravenous injection (Taylor, 1986). Osteoblastic osteosarcomas developed in dogs after inhalation of a monodisperse ^{241}Am aerosol (Gillett *et al.*, 1985).

3.1.13 Curium-244

Skeletal cancers were observed in rats exposed by intravenous injection (Taylor, 1986) to ^{244}Cm, and lung and liver cancers in rats exposed by inhalation (Sanders & Mahaffey, 1978; Lundgren *et al.*, 1997).

3.1.14 Californium-249 and californium-252

Skeletal cancers were observed in mice given ^{249}Cf or ^{252}Cf intraperitoneally (Taylor *et al.*, 1983), and in dogs treated intravenously (Lloyd *et al.*, 1994c).

3.2 Studies published since the previous *IARC Monograph*

Table 3.1 summarizes published studies that relate to the measurement of radiation-induced cancer from incorporated α-particle emitters in experimental animals. Also included are references that were omitted from the previous *IARC Monograph*, but considered important to include here.

In all of the studies in Table 3.1, at least one target tissue or organ was shown to have a statistically significant increase in the incidence of cancer that could be attributed to the incorporated radionuclide. Typically, the target organ receiving the largest dose incurred the formation of tumours.

3.2.1 Radon-222

(a) Rat

Using significant numbers of animals exposed to ^{222}Rn and progeny, both Monchaux & Morlier (2002) and Collier *et al.* (2005) investigated the interplay between total exposure and exposure rate for chronic inhalation of ^{222}Rn and progeny

Table 3.1 Studies in experimental animals exposed to radionuclides internally deposited

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Polonium-210				
Syrian hamsters (M) Lifespan Little *et al.* (1985), Shami *et al.* (1982)	Intratracheal instillation ^{210}Po carrier-free	Lung:	Statistical analysis of difference between groups (P 0.02–0.05)	
	2.4 Gy at 16 mGy/d (120 d average to deliver 80%)	14/62 (23%)		
	2.4 Gy at 32 mGy/d (60 d of dose)	15/69 (25%)		
	2.4 Gy at 192 mGy/d (10 d of dose)	26/58 (45%)		
	once/wk for 15 wk			
	1 ^{210}Po instillation only	2/41 (5%)		
	Control	0		
	240 mGy at 1.6 mGy over 120 d, 15 instillations	6/68 (9%)		
	240 mGy at 19 mGy, 1 instillation over 10 d	1/85 (1%)		
	saline only instillation	0		
	Animals/group at start (NR)			
Radon-222				
Rat, Sprague Dawley (M) 1–12 mo Monchaux & Morlier (2002)	Chronic inhalation ^{222}Rn and progeny: Groups: 1 (105 WLM, 188 WL); 2 (107, 147); 3 (100, 58); 4 (100, 13); 5 (100, 152); 6 (42,18); Controls	Lung (malignant tumours, %): 7.1, 2.8, 4.2, 5.4, 1.6[a], 1.2[a], 0.6	Data combined from CEA & AEA-Technologies studies.	
	Group 0: 120 unexposed controls Group 00: 120 sham-exposed controls 785 historical controls; 120–240 exposed animals/group	No lung cancer was observed in controls	[a] Not statistically different from controls	
Rat, Sprague Dawley (M) Lifespan Collier *et al.* (2005)	Chronic inhalation, ^{222}Rn and progeny (attached fraction > 98.5%)	Lung (primary tumours):		
	Study 1 (1000 WL): 200, 400, 800, 1 600, 3 200 WLM	Study 1–8/156 (5%); 1/111 (1%); 2/97 (2%); 8/102 (8%); 6/34 (18%)	$P < 0.005$	
	Study 2 (1000 WLM): 250, 500, 1 000, 2000 WL	Study 2–8/46 (17%); 3/46 (6.5%); 7/46 (15%); 11/52 (21%)	$P < 0.005$	
	Study 3 (100 WLM): 15, 150, 1 000 WL	Study 3–5/190 (3%); 6/186 (3%); 3/182 (2%); 4/82 (2%)	$P < 0.05$	
	46–190 animals/group			

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Radium isotopes				
Dog, beagle (M, F) Lifespan Lloyd *et al.* (2000a)	i.v. injection $^{226}RaCl_2$.: 0.275, 0.651, 2.31, 6.13, 12.5, 39.6, 119, 383 kBq/kg; 1 × at 1.5 yr 10–25 animals/group	Osteosarcomas: 0/10; 2/25 (8%); 2/23 (8.7%); 1/14 (7.1%); 5/13 (38.5%); 11/12 (91.7%); 12/13 (92.3%); 9/10 (90%)	$P < 0.2$	
	i.v. injection $^{228}RaCl_2$.: 0.656, 1.83, 5.68, 11.1, 34.5, 96.8, 306 kBq/kg; 1x at 1.5 yr 7–13 animals/group	Osteosarcomas: 0/12; 1/13 (7.7%); 10/12 (83.3%); 9/12 (75%); 12/12 (100%); 6/8 (75%); 1/7 (14%)	$P < 0.2$	
Dog, beagle (M, F) Lifespan Taylor *et al.* (2000)	i.v. injection, single $^{226}RaCl_2$. Dose to intraocular melanotic tissue, Gy 0; 0.93; 2.23; 5.59; 7.08; 21.01; 31.58; 67.47 9–25 animals/group; 132 controls	Intraocular melanomas: 1/132 (1%); 1/25 (4%); 3/22 (14%); 5/12 (42%); 1/12 (6%)		
Thorium-228				
Dog, beagle (M, F) Lifespan Lloyd *et al.* (2000a)	i.v. injection ^{228}Th citrate. 0.063, 0.192, 0.560, 1.12, 3.40, 10.7, 31.8, 99.7 kBq/kg; 1 × at 1.5 yr 2–13 animals/group	Osteosarcomas 0/13; 1/12 (8.3%); 5/12 (41%); 11/13 (77%); 12/12 (100%); 12/12 (100%); 2/4 (50%)	$P < 0.2$	
Thorium-232 (Thorostrast)				
Rat, Wistar (M) Lifespan Hahn *et al.* (2002)	i.m. implantation, $^{232}ThO_2$ (Thorotrast) 2 × (0.05 mL, 25% suspension), 2 injections 50 animals/group	Soft-tissue wound site tumours: 0; 25/50 (50%)	Th vs DU $P < 0.0014$	
Depleted uranium				
Rat, Wistar (M) Lifespan Hahn *et al.* (2002)	IM implantation, DU metal. Groups: Surgical control; Tantalum metal (5 × 5 × 1.1mm) wafer implant control; DU (1mm x 2mm) 4 pellets; DU (2.5 × 2.5 × 1.5mm) 4 wafers; DU (5 × 5 × 1.5mm) 4 wafers 50 animals/group	Soft-tissue wound site tumours: 0; 2/50 (4%); 0; 3/50 (6%); 9/49 (18%) Kidney tumours: 0; 0; 1/50 (2%); 1/50 (2%); 2/49 (4%)	Incidence of kidney tumour considered equivocal Th > DU 5.0 × 5.0mm; $P < 0.0014$ DU 5.0 × 5.0mm > sham cont.; $P = 0.0012$ DU 5.0 × 5.0mm > Ta; $P < 0.0028$	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Uranium citrate				
Mouse, CBA/H (M) Ellender *et al.* (2001)	Multiple i.p. injections (9 over 3 wk) ^{233}U citrate (average bone doses calculated to 500 days after administration) 0; 0.2-0.3; 0.5-1.0; 1.3-1.6 Gy; 50–100 animals/group; 100 controls	Osteosarcomas: 2/88 (2%); 2/91 (2%); 1/54 (2%); 1/48 (2%) Myeloid leukaemia: 0; 4/91 (4%); 2/54 (4%); 2/48 (4%) Hepatocellular carcinomas: 38/88 (43%); 52/91 (57%); 29/54 (54%); 26/48 (54%)		
Neptunium-237				
Rat, Sprague Dawley (M) Lifespan Dudoignon *et al.* (2001)	795 controls; 109 controls from a previous study Single inhalation (nose-only), $^{237}NpO_2$. ILD groups (Bq): 0, 90, 190, 740, 1 480, 2 560, 4 070. Corresponding mean lung doses (Gy). 0, 0.5, 1.1, 4.1, 7.7, 14.5, 36.4 12–102 animals/group	Lung tumour incidence* (% rats with tumours): 0.6, 17.6, 23.5, 62.6; 66.7, 75.0, 91.7		Mean survival (SD) d 778 (109), 735 (130), 748 (129), 725 (117), 727 (119), 698 (109), 627 (92). *Scoring included neoplastic and preneoplastic lesions
Rat, Sprague Dawley (M) Lifespan Dudoignon *et al.* (2003)	Single inhalation $^{237}NpO_2$. Mean dose Gy(sd): 0, 0.5 (0.1), 1.1, (0.3), 4.1 (0.9), 7.7 (1.4), 14.5 (3.3), 36.4 (10.2) 12–102 animals/group; 785 controls; 109 controls from a previous study	Lung carcinoma incidence: 5/785 (0.6%); 1/33 (3%); 7/102 (7%); 8/24 (33%); 9/23 (39%); 23/24 (96%); 18/12 (150%)		Animals with > 1 tumour Experimental study same as Dudoignon *et al.* (2001) except with complete histopathology
Plutonium oxide				
Rat, Sprague Dawley (M) Lifespan Dudoignon *et al.* (2003)	Single inhalation $^{239}PuO_2$. ILD groups (Bq): 0, 410, 600, 810, 1310, 2230, 3450. Corresponding mean lung doses (Gy). 0, 2.5, 3.6, 5.0, 8.2, 14.0, 22.5 26–31 animals/group; 795 controls, 109 controls from previous studies	Lung carcinoma incidence: 5/795 (0.6%); 2/30 (7%); 2/28 (7%); 3/31 (10%); 8/35 (23%); 7/26 (27%); 10/26 (38%)		Mean survival (SD) Scoring included neoplastic and preneoplastic lesions 778 (109), 796 (119), 756 (167), 788 (128), 768 (123), 731 (147), 754 (133) Animals with > 1 tumour Experimental study same as Dudoignon *et al.* (2001) except with complete histopathology

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (F) Lifespan Oghiso & Yamada (2003a)	Inhalation, single, $^{239}PuO_2$, lung dose Gy (SD): 0; 0.16(0.05), 0.45(0.24), 1.59(0.32), 2.76(0.43), 4.76(0.24), 5.43(0.29), 6.61(0.28), 8.52(0.67) 30–134 animals/group; 206 controls	Lung (malignant tumour): 1/206 (0.5%); 1/80 (1.2%); 12/134 (9%); 60/128 (47%); 78/126 (62%); 32/40 (80%); 27/31 (87%); 28/31 (90%); 27/30 (90%)	$P < 0.001$	
Dog, beagle, young adult (M, F) Lifespan Muggenburg *et al.* (2008)	Single Inhalation, $^{239}PuO_2$ monodisperse aerosols (0.75,1.5, 3.0 μm AMAD). Exposure groups (median ILB, kBq ^{239}Pu lung burden/kg body mass): 0, 0.16, 0.63, 1.6, 3.7, 6.4, 14, 29. Lung doses to death depend on particle size group 10–21 animals/sex/group; 18 controls/sex/group; 142 controls from a previous study	Lung (tumours): 4/36 (11%); 8/21 (38%); 25/37 (68%); 39/42 (93%); 29/33 (88%); 20/31 (65%); 4/27 (15%); 0		Median age at death (d) 4865, 4637, 3152, 2079, 1413
Plutonium citrate				
Mouse C3H/HeN, C57BL/6J, $B6C3F_1$ (F) Lifespan Oghiso & Yamada (2003b)	Single IP injection ^{239}Pu citrate. Injected dose (kBq). C3H: 0, 0.1, 0.5, 1.0, 5.0, 10.0 C57BL/6: 0, 0.1, 0.5, 1.0, 5.0, 10.0 $B6C3F_1$: 0, 0.1, 0.5, 1.0, 5.0, 10.0 30–60 animals/group	Osteosarcomas incidence (%): 0; 4/30 (13.3%); 19/30 (63.3%); 14/30 (46.7%); 15/32 (46.9%); 8/30 (26.7%) 0; 3/30 (10%); 7/31 (22.6%); 16/32 (50%); 12/31 (38.7%); 4/30 (13.3%) 0; 8/31 (25.8%); 17/33 (51.5%); 12/33 (36.4%); 10/32 (31.2%); 11/32 (34.4%)	$P < 0.001$	
Mouse, C3H, C57BL/6, $BC3F_1$ (F) Lifespan Oghiso & Yamada (2000)	Single IP injection. ^{239}Pu citrate. Skeleton doses to death Gy (SD) C3H mice: 0, 0.68(0.04), 2.71(0.36), 4.42(0.58), 16.3(2.1) C57BL/6: 0, 0.63(0.06), 2.66(0.43), 4.08(0.69), 18.3(2.0) $B6C3F_1$: 0, 0.63(0.06), 2.62(0.37), 4.38(0.51), 16.8(1.8) 30–60 animals/group	Osteosarcomas incidence (%): C3H–0; 7/30 (23.3%); 19/30 (63.3%); 14/30 (46.7%); 12/30 (40%) C57BL/6–0; 4/30 (13.3%); 7/30 (23.3%); 16/30 (53.3%); 20/30 (66.7%) $BC3F_1$–1/60 (1.7%); 9/30 (30%); 17/30 (56.7%); 13/30 (43.3%); 10/30 (33.3%)		

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Dog, beagle (M, F) Lifespan Lloyd *et al.* (2001)	i.v. injection ^{239}Pu citrate. Dose groups (kBq/kg body mass): 0, 0.026, 0.067, 0.201, 0.382, 0.576, 1.77, 3.52, 11.0, 33.6, 106 8–46; 132 controls	Osteosarcoma incidence: 1/132 (1%); 1/28 (4%); 2/46 (4%); 4/38 (10%); 8/38 (21%); 10/26 (38%); 10/14 (71%); 10/12 (83%); 12/12 (100%); 12/12 (100%); 7/8 (87%)		
Plutonium nitrate				
Mouse, CBA/H (M) Lifespan Ellender *et al.* (2001)	Multiple i.p. injections (9 over 3 wk) ^{239}Pu citrate. Dose groups (Gy to 500 d). 0, 0.2, 0.5, 1.3 50–100 animals/group	Osteosarcoma incidence: 2/88 (2%); 2/97 (2%); 6/55 (11%); 18/124 (15%): Myeloid leukaemia 0; 4/97 (4%); 3/55 (6%); 11/124 (9%) Hepatocellular carcinomas: 38/88 (43%); 55/97 (60%); 43/55 (78%); 72/124 (58%)	$P < 0.001$	
Americium citrate				
Mouse, CBA/H (M) Lifespan Ellender *et al.* (2001)	Multiple i.p. injections (9 over 3 wk) ^{241}Am citrate. Dose groups (Gy to 500 d). 0, 0.3, 0.9, 1.6 at 12 wk 50–100 animals/group	Osteosarcoma incidence: 2/88 (2%); 0; 4/143 (3%); 10/48 (21%) Myeloid leukaemia: 0; 4/93 (4%); 12/143 (8%); 5/48 (10%) Hepatocellular carcinomas: 38/88 (43%); 45/93 (48%); 90/143 (63%); 36/48 (75%)	$P < 0.001$	
Curium–242				
Mouse, CBA/Ca (F) Lifespan Priest *et al.* (2006)	Inhalation single ^{242}Cm in FAP. Mean dose to lung Gy (5%, 95% CI) 120–160 animals/group 0, A1: 0.55(0.37–0.76); A2: 1.55(1.04–2.15); A3: 2.67(1.79–3.70); A4: 4.69(3.15–6.49)	Lung (malignant tumours): 105/371 (28%); 44/111 (40%); 49/113 (44%); 55/100 (55%); 58/112 (52%)	A1 vs control $P < 0.05$ A3 vs control $P < 0.05$	

AMAD, activity median aerodynamic diameter; CI, confidence interval; d, day or days; DU, depleted uranium; F, female; FAP, fused aluminosilicate particle; ILB, initial lung burden; ILD, initial lung deposit; i.m., intramuscular; i.p., intraperitoneal; i.t., intratracheal; i.v., intravenous; M, male; mo, month or months; NR, not reported; Ta, tantalum; vs, versus; wk, week or weeks; yr, year or years

in non-smoking rats. The results of both studies, plus previous data from other experiments, were consistent in demonstrating that for high cumulative exposures (about 1000 WLM), the tumour risk increases with increased exposure duration, and therefore decreased exposure rate (the so-called inverse dose–rate effect). However, for low cumulative exposure (> 100 WLM), increased exposure duration or decreased exposure rate decreased lung cancer risk. This biphasic response is important to consider when applying data from high exposure rate populations (such as some of the uranium miner cohorts) to low exposure rate groups (exposure in indoor environments).

3.2.2 Polonium-210

(a) Hamster

By varying the number of repeated intratracheal instillations that contained ^{210}Po, Little *et al.* (1985) were able to show that frank malignant lung tumour incidence increased with increasing dose rate. All groups received the same total dose to the lung (Table 3.1). For these groups, the total number of instillations was kept constant by substituting instillation of equal volumes of isotonic saline when no ^{210}Po was administered. Of significant note was the decreased tumour incidence for a group in which a single ^{210}Po instillation was administered without accompanying saline instillations. This result reinforced the conclusions of Shami *et al.* (1982) who demonstrated the importance of the saline administrations given after ^{210}Po in increasing lung tumour incidence.

3.2.3 Radium isotopes

(a) Dog

The study results on osteosarcomas induced by ^{226}Ra in dogs shown in Table 3.1 and reported by Lloyd *et al.* (2000a) are similar but not identical to those previously published by the same authors in 1993 (different number of study animals, different percentage incidence values). However, the differences do not affect the interpretation of the results, i.e. that the dose–response for osteosarcoma induction for ^{226}Ra is a linear response over the study dose range (Lloyd *et al.*, 1993). The bone cancer data for intravenous ^{228}Ra in dogs (Lloyd *et al.*, 2000a) appeared to be new, but the authors did not analyse the dose–response relationship. However, in an earlier paper, Lloyd *et al.* (1997a) concluded that for equal skeletal radiation doses, ^{228}Ra would produce twice as many osteosarcomas as would ^{226}Ra, i.e. a toxicity ratio of 2.

Additionally, Taylor *et al.* (2000) showed that intravenous ^{226}Ra in dogs resulted in an increased incidence of eye melanoma. The incidence was monotonically dose-related over a range of 0.9–5.6 Gy (dose to intraocular melanotic tissue), but decreased with higher doses so that at 21 Gy and above, no melanomas were observed.

3.2.4 Thorium-228

(a) Dog

The study results on osteosarcoma incidence induced by ^{228}Th in dogs shown in Table 3.1 and reported in Lloyd *et al.* (2000a) are essentially identical to the results previously published by Mays *et al.* (1987). The toxicity ratio for ^{228}Th compared with ^{226}Ra is 8.5 (Lloyd *et al.*, 1997b), which is similar to that of its first progeny ^{224}Ra (toxicity ratio of 6 for single injection, 16 for repeated administration).

3.2.5 Thorium-232 (Thorostrast)

(a) Rat

Hahn *et al.* (2002) used an intramuscularly implanted Thorotrast suspension as a positive tumour control for their study of the carcinogenicity of depleted uranium metal fragments in rats. Thorotrast has been known to cause granulomas in humans when the Thorotrast extravasated from the intravenous injection site,

and infiltrated local soft tissue (Dahlgren, 1967; Liebermann *et al.*, 1995). A single dosage of 0.05 mL of a 25% suspension of Thorotrast injected into each biceps femoris of rats induced a 50% lifetime soft-tissue tumour incidence (Hahn *et al.*, 2002).

3.2.6 Depleted uranium

(a) Rat

Hahn *et al.* (2002) reported that intramuscular implantation of depleted uranium pellets in rats produced malignant soft-tissue tumours (fibrous histiocytoma, fibrosarcoma, osteosarcoma, in decreasing order) at the site of implantation, and with incidence that increased with increasing size of the implant. The dose–response relationship could not be directly linked to the radiation dose from uranium because of the confounding from varying implant sizes as well as varying amounts of uranium corrosion products at the implant site. No other significant cancers were found.

3.2.7 Neptunium-237

(a) Rat

Dudoignon *et al.* (2001, 2003) measured the incidence of lung cancer in rats that received a single inhalation exposure to respirable $^{237}NpO_2$ aerosols. Against radiation dose to the lung, the incidence of cancer had a linear dose–response from 0.5 to 36 Gy, and the relative effectiveness for producing lung cancer per unit dose was 3.3 times greater for neptunium than it was for plutonium.

3.2.8 Plutonium-239

(a) Plutonium Oxide ($^{239}PuO_2$)

(i) Rat

Dudoignon *et al.* (2001, 2003) measured the incidence of lung cancer in rats that received a single inhalation exposure to $^{239}PuO_2$. The incidence of cancer had a linear dose–response from 2.5 to 22 Gy.

Oghiso & Yamada (2003a) exposed rats by inhalation to polydisperse $^{239}PuO_2$ aerosols and followed the animals for lifespan. Their results showed dose-dependent survival reduction that was correlated with increased malignant lung tumours at doses over 0.45 Gy, reaching a maximum incidence of 90% at 6.6–8.5 Gy. They also noted that the relative effectiveness for 50% lung carcinoma incidence was about 11 times higher than for single thoracic irradiation with X-rays.

(ii) Dog

In an experiment designed to study the "hot particle hypothesis" for inhaled α-particle emitting radionuclides, Muggenburg *et al.* (2008) exposed dogs by single inhalation to monodisperse aerosols of $^{239}PuO_2$ of three different particle sizes (0.75, 1.5, 3.0 μm Activity Median Aerodynamic Diameter). In so doing, the relationships between average dose and dose rate to the lung could be compared to local dose rate around each plutonium particle, and the fraction of lung tissue irradiated. Based on the lung doses achieved in the study, which ranged from about 1 to 60 Gy, significant incidences of lung cancer were observed for all particle size groups, and there were good dose–response relationships. Comparison of the particle-size-specific groups indicated that a more uniform distribution of α-particle radiation dose within the lung had an equal or possible greater risk of neoplasia than less uniform distributions of radiation dose. These results are consistent with those from other

studies in which the uniformity of α-particle radiation dose was also compared.

(b) Plutonium Citrate (^{239}Pu Citrate)

(i) Mouse

Oghiso & Yamada (2003b) compared the bone tumour incidences for three strains of mice (C3H/He, C57BL/6, B6C3F$_1$) injected with varying doses of ^{239}Pu Citrate, and found that the dose–response patterns did not appear to differ among the three strains. Both tumour type and location of tumours were also similar. No other types of cancer were found in the mice, indicating that osteosarcoma is the only specific plutonium-induced tumour in mice. These results are in broad agreement with those of a previously published study by the same authors, using the same mouse strains (Oghiso & Yamada, 2000), but differ from results obtained using CBA mice (Humphreys *et al.*, 1987).

(ii) Dog

Lloyd *et al.* (2001) updated the bone tumour incidence in dogs injected intravenously with ^{239}Pu Citrate published previously in Lloyd *et al.* (2000b), and showed a linear dose–response of osteosarcoma incidences versus average dose to the bone 1 year before death. ^{239}Pu was 16 times more effective than ^{226}Ra in producing bone tumours when compared, based on average skeletal dose. In an earlier paper, Taylor *et al.* (1991) also showed that injected ^{239}Pu caused liver cancer.

(c) Plutonium nitrate

Ellender *et al.* (2001) injected ^{239}Pu, ^{241}Am or ^{233}U intravenously into a different strain of mouse (CBA/H), and followed the animals for lifespan. There were clear dose–response-related incidences of osteosarcoma for the mice injected with either ^{239}Pu or ^{241}Am, with the former being about twice as carcinogenic per unit dose to bone; ^{233}U on the other hand showed little ability to increase bone cancer rates, and there was no dose–response relationship. For myeloid leukaemia, there was little, if any, difference in the increased incidence of the leukaemia for ^{239}Pu, ^{241}Am or ^{233}U, but the incidences were statistically significant, as determined using Cox hazard modelling. Significant increases in renal and hepatic carcinomas were also observed for the mice exposed to ^{233}U and ^{241}Am, respectively, but not for the other injection groups. The lack of consistent findings for the three radionuclides for tumours of the kidney and liver make the positive results uncertain, particularly in view of the significant incidence of disease in the control animals. Additionally, although the finding of a small but significant incidence of myeloid leukaemia in the CBA mouse has been repeatedly demonstrated with both radionuclides and external radiation, the results should be interpreted cautiously in view of the lack of observed leukaemia in other strains of mice that are known not to be sensitive to the induction of acute myeloid leukaemia (e.g. Oghiso & Yamada 2000, 2003b), and other species such as the dog (Lloyd *et al.*, 2001, 2004).

3.2.9 Curium-242 in insoluble form

(a) Mouse

Priest *et al.* (2006) exposed mice to either ^{45}Ca-FAP or ^{242}Cm-FAP [FAP; Fused Aluminosilicate Particles] aerosols by inhalation to study the relative ability of β-particles or α-particles in producing lung cancer when given in inhaled amounts that would result in relatively equivalent absorbed doses to the lung (i.e. a RBE study). There were four radiation dose groups ranging from about 0.5 Gy to about 5 Gy. Although there was an increased incidence of malignant lung tumours in the two highest dose groups for both radionuclides, only the ^{242}Cm in the lowest two groups had elevated cancer rates. It should be noted that the control lung cancer incidence was about 28% for these CBA/Ca mice. No other cancers of significance were noted, which was

expected given the relative insolubility of the aerosol carrier particles (FAP).

3.3 Other studies

Selby & Priest (2005) tested the hypothesis that male mice injected with ^{239}Pu Citrate would transmit mutations leading to somatic effects in their offspring by breeding ^{239}Pu-contaminated male CBA/Ca mice with uncontaminated females. Absorbed doses to the testes were calculated to be 0.3 and 4 Gy in the two experimental groups. After following the offspring for their lifespan, no evidence was found for leukaemia induction or any other probable causes of death. Interestingly, male progeny from both treated dose groups lived significantly longer than those from the controls.

Miller *et al.* (2003) compared the locations of osteosarcomas in ^{239}Pu-injected dogs with those described in studies of the Mayak workers who also had osteosarcomas. An almost identical distribution of ^{239}Pu-induced sarcomas was found for both populations, i.e. about 70% of the tumours were found in the axial skeleton. This distribution differs from that of naturally occurring sarcomas, in which about 60% of bone tumours occur in the peripheral or apendicular skeleton. These results support the model that plutonium retention and sarcomas have a preference for well vascularized, cancellous bone sites.

3.4 Synthesis

Several studies on the carcinogenic effects of α-particle-emitting radionuclides in experimental animals have appeared in the literature since the publication of the previous *IARC Monograph* (IARC, 2001). These include new data or data reanalysed from previous studies on ^{210}Po, ^{222}Rn, ^{226}Ra, ^{228}Th, ^{232}Th, ^{233}U, ^{237}Np, ^{239}Pu, ^{241}Am, and ^{242}Cm. Routes of exposure include intravenous or intraperitoneal injection, intramuscular implantation, intratracheal instillation, and inhalation, and species include mice (four strains), rats (two strains), Syrian hamsters, and beagle dogs. The data from these studies consistently support and confirm the conclusions that all of the studied α-particle-emitting radionuclides are clearly carcinogenic in experimental animals. Because the patterns of radiation dose for these α-particle emitters are typically non-uniform and specific to different tissues and organs, the site-specific cancer incidences vary based on the radionuclide, its physicochemical form, route of administration, and to a lesser degree, on the experimental animal.

It is likely that other α-particle-emitting radionuclides not included above also may be carcinogenic to the tissues and organs in which they are capable of depositing; however, lacking experimental evidence, it is not possible to indentify them explicitly.

4. Other Relevant Data

See Section 4 of the *Monograph* on X-radiation and γ-radiation in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of radon-222 and its decay products. Radon-222 and its decay products cause cancer of the lung. Also, a positive association has been observed between exposure to radon-222 and leukaemia.

There is *sufficient evidence* in humans for the carcinogenicity of underground haematite mining with exposure to radon. Underground haematite mining with exposure to radon causes cancer of the lung.

There is *sufficient evidence* in humans for the carcinogenicity of radium-224. Radium-224 causes bone sarcomas.

There is *sufficient evidence* in humans for the carcinogenicity of radium-226. Radium-226 causes bone sarcomas and carcinomas of the paranasal sinuses and mastoid process.

There is *sufficient evidence* in humans for the carcinogenicity of radium-228. Radium-228 causes bone sarcomas.

There is *sufficient evidence* in humans for the carcinogenicity of thorium-232 as stabilized thorium-232 dioxide in colloidal form (Thorotrast). Diagnostic injection of Thorotrast causes primary liver cancer, leukaemia (excluding chronic lymphocytic leukaemia), cancer of the extrahepatic bile ducts, and of the gallbladder. Also, positive associations have been observed between injection of Thorotrast and cancer of the pancreas and of the prostate.

There is *sufficient evidence* in humans for the carcinogenicity of plutonium-239. Plutonium-239 causes cancer of the lung, liver and bone.

There is *limited evidence* in humans for the carcinogenicity of mixtures of uranium isotopes.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ^{210}Po, ^{222}Rn, ^{224}Ra, ^{226}Ra, ^{228}Th, ^{230}Th, ^{232}Th, ^{233}U, $^{234, 235, 238}$U (natural, enriched and depleted uranium), ^{237}Np, ^{238}Pu, ^{239}Pu, ^{241}Am, ^{244}Cm, ^{249}Cf, ^{252}Cf.

The radionuclide ^{228}Ra may be considered a mixed β-particle emitter in two-year carcinogenicity bioassays with rodents (with truncation of the decay chain at ^{228}Th; half-life, 1.91 years), whereas the effects of α-particle radiation predominate in long-term human exposure.

Radon-222 with its decay products are *carcinogenic to humans (Group 1).*

Radium-224, radium-226, radium-228 are *carcinogenic to humans (Group 1).*

Thorium-232 (as Thorotrast) is *carcinogenic to humans (Group 1).*

Plutonium-239 is *carcinogenic to humans (Group 1).* The Working Group noted that human exposure to plutonium-239 may also include exposure to other plutonium isotopes.

Underground haematite mining with exposure to radon is *carcinogenic to humans (Group 1).*

Internalized radionuclides that emit α-particles are *carcinogenic to humans (Group 1).*

In making this overall evaluation, the Working Group took into consideration the following:

- α-Particles emitted by radionuclides, irrespective of their source, produce the same pattern of secondary ionizations, and the same pattern of localized damage to biological molecules, including DNA. These effects, observed *in vitro*, include DNA double-strand breaks, chromosomal aberrations, gene mutations, and cell transformation.
- All radionuclides that emit α-particles and that have been adequately studied, including radon-222 and its decay products, have been shown to cause cancer in humans and in experimental animals.
- α-Particles emitted by radionuclides, irrespective of their source, have been shown to cause chromosomal aberrations in circulating lymphocytes and gene mutations in humans *in vivo*.
- The evidence from studies in humans and experimental animals suggests that similar doses to the same tissues — for example lung cells or bone surfaces — from α-particles emitted during the decay of different radionuclides produce the same types of non-neoplastic effects and cancers.

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