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RADIOACTIVE MATERIAL

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INTERNALIZED β-PARTICLE EMITTING RADIONUCLIDES

Internalized radionuclides that emit β-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 Pure β-particle emitters

2.1.1 Tritium

^{3}H is a radioactive isotope of hydrogen that emits low-energy β-particles. ^{3}H is readily taken into the body via inhalation, ingestion, and dermal absorption; once deposited in the body, ^{3}H acts as an internal emitter. While ubiquitous, the low magnitude of ^{3}H doses typical of environmental and occupational settings makes epidemiological research on the health effects of ^{3}H intakes difficult. Large studies are required to derive estimates with statistical stability, confounding must be minimized in order not to obscure or bias estimates of association that are often modest in low-dose settings, and exposure assessment must be of high quality to minimize bias due to measurement error. These requirements need to be given due consideration when evaluating the evidence on the carcinogenicity of β-particle irradiation arising from ^{3}H intakes.

The current review of the epidemiological literature focuses on studies of workers in the nuclear power and weapons industry for whom ^{3}H could have been an important contribution to the dose. While environmental releases of ^{3}H have led to large numbers of people exposed to low levels of ^{3}H, there have been few epidemiological studies of these exposures, and none has quantified doses from ^{3}H. This review gives primary attention to epidemiological analyses in which individuals' ^{3}H exposures were quantified permitting comparisons between groups with different exposure histories.

Several studies have considered the risk of prostate cancer and occupational exposures to radionuclides, including ^{3}H, among United Kingdom nuclear industry workers. Rooney *et al.* (1993) reported on a case–control study of UKAEA (United Kingdom Atomic Energy Authority) workers with follow-up through 1986, noting a significantly elevated relative risk of prostate cancer among workers with

documented intake of ^{3}H (RR, 14.26; 95%CI: 3.09–133.16). The excess was primarily associated with work in heavy-water reactors, and the risk of prostate cancer increased with increasing level of potential exposure to ^{3}H (*P* for trend < 0.05). Carpenter *et al.* (1998) examined cancer mortality in relation to monitoring for internal exposure to ^{3}H and other radionuclides among employees of three different cohorts: UKAEA, AWE (Atomic Weapons Establishment), and the Sellafield plant of British Nuclear Fuels Limited, all in the United Kingdom. Overall cancer mortality was significantly below national rates among workers monitored for ^{3}H exposure, but relative risks for prostate cancer increased with the number of years of exposure for those monitored for ^{3}H relative to those not monitored for any radionuclide: 1 year (RR, 0.31), 2–4 years (RR, 3.19), and 5+ years (RR, 2.26) of ^{3}H exposure. Atkinson *et al.* (2007) reported on a further analysis of prostate cancer among UKAEA workers including deaths up through 1997 (Atkinson *et al.*, 2007). ^{3}H doses were not quantified but information on ^{3}H-monitoring status was collected. Among workers monitored for ^{3}H, the initial finding for the increased risk of prostate cancer was confirmed (RR, 5.80; 95%CI: 2.15–15.66) but only a small excess was observed in the later period (RR, 1.20; 95%CI: 0.59–2.41).

Lung cancer incidence among 95430 males in the Canadian National Dose Registry was positively associated with radiation dose (Hazelton *et al.*, 2006). This study used a two-stage clonal expansion model to assess the effect of γ-radiation and tritium dose on lung cancer risk. [It was noted that although whole-body tritium exposures are generally small in comparison with gamma exposures, the dose–response for tritium considered separately was marginally significant.]

Several other cohort studies of nuclear industry workers have examined associations between radiation and cancer among nuclear industry workers incorporating ^{3}H dose estimates into whole-body dose estimates, but without conducting separate analyses examining the ^{3}H component of the whole-body dose (e.g. Wing *et al.*, 1991; Cragle & Watkins, 1998; McGeoghegan & Binks, 2001; Zablotska *et al.*, 2004; Cardis *et al.*, 2007; Richardson & Wing, 2007; Schubauer-Berigan *et al.*, 2007). Given the relatively small contribution of ^{3}H to whole-body dose in these cohorts, these studies provide little information about the risk specifically associated with ^{3}H intake.

The impact of releases to the environment on cancer rates have been the subject of investigations around various nuclear facilities, including several that released ^{3}H: the Savannah river site (Grosche *et al.*, 1999), the Krümmel facility (Grosche *et al.*, 1999), and several Canadian facilities (McLaughlin *et al.*, 1993). None of these studies included estimates of ^{3}H dose.

2.1.2 Phosphorus-32

^{32}P is a pure β-particle emitter with a physical half-life of 14.3 days. ^{32}P has been used as a therapeutic radiopharmaceutical for conditions including *polycythaemia vera* (Vinjamuri & Ray, 2008). Administered activities of ^{32}P are in the range of 1.85–2.96 × 10^{8} Bq, and estimates of the average skeletal dose of 300 rad per 7.4 × 10^{8} Bq [4 nGy/Bq] administered have been observed (IARC, 2001).

These doses far exceed the relatively low doses typical of occupational and environmental settings where people are internally exposed to other β-particle emitters, such as ^{3}H. While avoiding the problems associated with epidemiological studies of low doses, patients with radiotherapy treatment often also receive non-radiological treatments, which may confound interpretations of ^{32}P effects, and treated patients may differ from the general population in terms of the risk of developing a malignancy due to the underlying condition being treated (e.g. *polycythaemia vera*), or differ in susceptibility to the carcinogenic effects of irradiation.

A study by Modan & Lilienfeld (1965) provided strong evidence for the leukaemogenic effect of ^{32}P. Modan and Lilienfeld compared the occurrence of leukaemia among *polycythaemia vera* patients treated by phlebotomy, X-irradiation only, ^{32}P only, or a combination of X-irradiation and ^{32}P. The incidence of acute leukaemia was 11% in the 228 patients treated with ^{32}P but less than 1% in the 133 non-irradiated patients treated by phlebotomy only. Furthermore, the risk of leukaemia increased with increasing doses of administered ^{32}P.

Subsequent publications have confirmed the high risk of leukaemia in *polycythaemia vera* patients treated by ^{32}P (Najean *et al.*, 1996; Parmentier, 2003; Finazzi *et al.*, 2005). However, the interpretation of findings regarding ^{32}P leukaemogenicity in the contemporary literature comparing treatment protocols for patients with *polycythaemia vera* has been complicated by the fact that contemporary treatments other than ^{32}P also may be leukaemogenic (Parmentier, 2003).

Finazzi *et al.* (2005) reported on a study of 1638 patients with *polycythemia vera* enrolled in the European Collaboration on Low-dose Aspirin in Polycythemia Vera project (Finazzi *et al.*, 2005). A total of 21 cases of acute myeloid leukaemia and one case of myelodysplastic syndrome with rapid progression to acute myeloid leukaemia were diagnosed after a median of 2.5 years (range, 0.5–4.1 years) from the registration, and 8.4 years from the diagnosis of *polycythemia vera*. Patients undergoing phlebotomy or interferon therapy as the only cytoreductive agent could potentially represent the natural risk for *polycythemia vera* patients to progress to acute myeloid leukaemia, and were therefore treated as a reference category. The incidence rate of acute myeloid leukaemia/myelodysplastic syndrome (AML/MDS) was similar to those treated with phlebotomy or hydroxyurea at registration (approximately 0.29 per 100 persons per year), whereas this rate was 1.8 per 100 persons per year in those receiving at least one alkylating agent or ^{32}P at recruitment. Treatment by ^{32}P was significantly associated with risk of AML/MDS (hazard ratio (HR), 8.96; 95%CI: 2.13–37.58).

2.2 Mixed exposures

2.2.1 Caesium-137

Fallout from weapons testing in the 1950s and from the Chernobyl accident resulted in increased ^{137}Cs activity concentration in reindeer muscles, particularly during the winter season (Ahman & Ahman, 1994), which was fairly well correlated with caesium deposition in the reindeer pastures of Sweden (Ahman *et al.*, 2001). Lapps who breed reindeer in the northern parts of the Nordic countries and the Russian Federation have ingested fallout products via the lichen–reindeer–man food-chain since the 1950s.

A cohort of 2034 Lapps reindeer breeders and members of their households was followed in Sweden for cancer incidence and mortality during 1961–85 (Wiklund *et al.*, 1990, 1991). Both cancer mortality and incidence rates for all cancers combined were lower than in the Swedish population as a whole (SMR, 0.70; 95%CI: 0.56–0.87; SIR, 0.61; 95%CI: 0.05–0.75). This may reflect a healthier lifestyle and lower smoking prevalence compared to the general population. The stomach was the only site for which a significantly increased risk for cancer was found (SIR, 2.25; 95%CI: 1.46–3.32) when compared with national rates. [This finding was attributed to high intake of salt and other dietary habits.]

2.2.2 Fission products

Persons exposed as a result of releases from nuclear facilities can receive external doses from fission-product radionuclides deposited in the environment as well as internal doses from the

ingestion of foods containing fission products such as ^{137}Cs and ^{90}Sr (IARC, 2001).

^{137}Cs and ^{134}Cs, along with ^{131}I, were the main contributors to the internal dose populations exposed as a result of the Chernobyl accident. ^{137}Cs and ^{134}Cs were also the most important radionuclides for external doses for these populations (IARC, 2001).

Several ecological studies have examined possible associations between the risk of malignancies, especially childhood leukaemia, and average doses from external and internal exposures from the Chernobyl fallout, including the European Childhood Leukaemia–Lymphoma Study (ECLIS), the largest and most comprehensive study to date (Parkin *et al.*, 1992, 1996). The ECLIS study found no evidence of a radiation-related increase in the incidence of leukaemia in Europe in the first 5 years after the accident.

An ecological study conducted in Belarus and Ukraine (Pukkala *et al.*, 2006) found a significant 2-fold increase in risk of breast cancer during 1997–2001, in the most contaminated districts (average cumulative whole-body dose from internal and external exposure of 40.0 mSv or more) compared to the least contaminated districts (RR in Belarus, 2.24; 95%CI: 1.51–3.32; and in Ukraine, 1.78; 95%CI: 1.08–2.93). [The Working Group noted that the assessment of doses in these districts considered the possibility that a portion of the diet could be from outside of those districts.]

Almost 30000 people living along the Techa River were exposed to a complex mixture of radionuclides, largely ^{90}Sr and to lesser extent to ^{137}Cs, from the Mayak plutonium production and separation facility in the Russian Federation. Liquid radioactive waste was discharged into this river (Degteva *et al.*, 1996, 2002). Bone marrow and bone surfaces received high doses as a result of ^{90}Sr deposition, and the lower gastrointestinal tract was exposed as a result of the transit of unabsorbed radionuclides, mainly ^{90}Sr. Doses to other organs were primarily from a combination of external γ-ray exposures and internal γ-radiation from ingested ^{137}Cs (Kossenko *et al.*, 2005). Excess relative risks (ERRs)/Gy for deaths from all-solid cancer was 0.92 (95%CI: 0.2–1.7), and those for leukaemia, excluding chronic lymphocytic leukaemia, was 6.5 (95%CI: 1.8–24) (Krestinina *et al.*, 2005). Analyses of solid cancer incidence resulted in a similar estimate (ERR/Gy, 1.0; 95%CI: 0.3–1.9; Krestinina *et al.*, 2007). Nuclear weapons testing and production has resulted in large collective doses to the world's population, typically at low dose rates of radiation from internal exposure to a mixture of radionuclides.

Exposures to ^{90}Sr were particularly notable in the region around the Techa River, in the southern urals. During 1949–56, radioactive wastes were discharged directly into the river. People living along the river received internal exposures from the ingestion of radionuclides; ^{90}Sr was the main contributor to the internal exposure (Ostroumova *et al.*, 2006).

A long-term follow-up study of a cohort of residents was conducted, suggesting that risks of cancer mortality and incidence increased with increasing estimated committed dose in this population. Internal doses were reconstructed according to radionuclide intakes (also reconstructed), age-specific metabolism models, and models for dose distribution in the body. External doses were also received in this population; the external dose diminished more rapidly and consistently with distance than the internal dose. Consequently, the external component of the dose accounted for 49% of the total dose in the upper Techa, but only 6% in the lower Techa region. Considering leukaemia excluding chronic lymphocytic leukaemia, risk increased significantly with total (OR/Gy, 4.6; 95%CI: 1.7–12.3), internal (OR/Gy, 5.4; 95%CI: 1.1–27.2), and external red bone marrow (RMB) doses (OR/Gy, 7.2; 95%CI: 1.7–30.0). When the internal and external components of the total RBM dose were included simultaneously in the model, the magnitude of the external dose associated with

leukaemia (OR/Gy, 5.6; 95%CI: 1.3–24.2) was larger than the magnitude of the internal dose associated with leukaemia (OR/Gy, 3.5; 95%CI: 0.7–19.0; Ostroumova *et al.*, 2006).

The impact of ^{90}Sr releases to the environment on cancer rates have been the subject of several ecological investigations, characterizing both changes in exposure from fallout over time as well as ecological correlations between temporal patterns in ^{90}Sr levels and childhood cancer rates (Gould *et al.*, 2000; Mangano *et al.*, 2000).

2.3 Mixed β-particle emitters–radioiodines

Most of the information on the association between cancer risk and iodine isotopes comes from studies of the consequences of the Chernobyl accident. Studies of other populations exposed as a result of fallout or of medical exposures are generally less informative.

2.3.1 Chernobyl

(a) Cancer of the thyroid

Cancer of the thyroid accounts for approximately 3% of the total cancer incidence in more developed regions and 1% in less developed areas of the world general population (Jemal *et al.*, 2011). Although this is a relatively rare tumour, in the past several decades incidence rates have been increasing in most developed countries (Ferlay *et al.*, 2002). Descriptive epidemiological studies show marked international variation in the incidence of cancer of the thyroid, with the highest incidence reported in The Republic of Korea and New Caledonia (Ferlay *et al.*, 2010a, b). The substantial variations among world populations strongly suggest that environmental factors play a key role in the etiology of this cancer.

Cancer of the thyroid is of great concern in radiation protection, because large numbers of people have been exposed to radioiodines, which concentrate mainly in the thyroid, through environmental sources or for medical reasons. Exposure to radioiodines, particularly ^{131}I, comes from atmospheric nuclear weapons tests, accidental or routine emissions from nuclear power plants, and nuclear weapons production facilities (UNSCEAR, 2000a). In medical settings, radioactive iodine is the treatment of choice for thyrotoxicosis, and a common treatment for cancer of the thyroid (Gross *et al.*, 1999).

Until the Chernobyl accident, however, the carcinogenic effect of exposure to ^{131}I was considered to be small compared to that of external photon exposures (UNSCEAR, 1994), and this was attributed to differences in radiation quality and particularly exposure rates (Shore, 1992). In fact, little experience of the effects in children of iodine isotopes on the thyroid was then available, as most studies on the carcinogenic effects of ^{131}I had been conducted in adult populations: the number of young people exposed in these studies was, however, small (Holm *et al.*, 1988; Hamilton *et al.*, 1989; Robbins & Adams, 1989; Rallison *et al.*, 1990). In one cohort study of 35000 Swedish patients examined with ^{131}I, a small, non-significant increase in risk of developing thyroid cancer was observed among the 7% of the cohort that had been exposed before the age of 20 (SIR, 1.69; 95%CI: 0.35–4.93; Hall *et al.*, 1996).

After the Chernobyl accident, a wide range of thyroid doses was received by the inhabitants of the contaminated areas in the three affected countries. Doses varied with age at the time of the accident (being highest in those who were youngest at the time of the accident), level of ground contamination, rate and source of milk consumption. Reported individual thyroid doses ranged up to several tens of Gy, and average doses ranged from a few tens of mGy to several Gy (UNSCEAR, 2000b; Cardis *et al.*, 2006).

Other sources of exposure resulting from the Chernobyl accident also contributed to thyroid dose, including the intake of short-lived radioiodines (^{132}I, ^{133}I, and ^{135}I) and radiotelluriums

(^{131}Te and ^{132}Te), external irradiation from radionuclides deposited on the ground, and ingestion of ^{134}Cs and ^{137}Cs. For most individuals, however, these represented only a small percentage of the thyroid dose in comparison to exposure to ^{131}I (UNSCEAR, 2000b; United Nations Chernobyl Forum, 2006)

(i) Exposures in childhood

The main health effect of radiation from the accident observed to date is a dramatic increase in the incidence of thyroid cancer in persons exposed in childhood and adolescence (United Nations Chernobyl Forum, 2006). This increase was observed first in the early 1990s in Belarus, and continues until now in the most contaminated areas of Belarus, Ukraine, and the Russian Federation (Kazakov *et al.*, 1992; Stsjazhko *et al.*, 1995; UNSCEAR, 2000b; Jacob *et al.*, 2006). In the whole of Belarus, by 1995, the incidence of childhood thyroid cancer had increased to 4 cases per 100000 per year compared to 0.03–0.05 cases per 100000 per year before the accident. As time has progressed, the incidence rate of childhood thyroid cancers has returned to pre-accident levels, with the exception of an increase in incidence in adolescents. The overall number of thyroid cancer cases diagnosed in Belarus, Ukraine and in the four most contaminated regions of the Russian Federation during 1986–2002 among those who were children or adolescents at the time of the Chernobyl accident is close to 5000 (Cardis *et al.*, 2006; United Nations Chernobyl Forum, 2006).

Several epidemiological studies of thyroid cancer following exposure to radioactive iodines from the Chernobyl accident have been reported both in the most contaminated countries and in other European countries (UNSCEAR, 2000b), providing compelling evidence that the observed increase is related to iodine fallout from the Chernobyl accident. Results of case–control (Astakhova *et al.*, 1998; Cardis *et al.*, 2005; Kopecky *et al.*, 2006) and cohort (Tronko *et al.*, 2006) studies with individual thyroid dose estimation are shown in Table 2.1 (available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-05-Table2.1.pdf), together with those of the most recent ecological study (Jacob *et al.*, 2006). Estimates from the larger case–control studies in Belarus (Astakhova *et al.*, 1998; Cardis *et al.*, 2005) and the Russian Federation (Cardis *et al.*, 2005) and the cohort study in Ukraine (Tronko *et al.*, 2006) are similar though slightly lower than the estimate from studies of external radiation (Ron *et al.*, 1995). The ERR/Gy derived in the ecological study (Jacob *et al.*, 2006) is higher than those derived from the larger case–control and cohort studies, but lower than that from the case–control study in the Bryansk area (Kopecky *et al.*, 2006). The latter estimate is based on a small number of cases (n = 66), most with doses much lower than 1 Gy, and the confidence intervals are wide, overlapping those of the other case–control and cohort studies. Dose-related increases in the risk of follicular adenoma of the thyroid were also observed in the Ukrainian screened cohort (Zablotska *et al.*, 2008).

There is some indication that iodine deficiency at the time of exposure may increase the risk of developing thyroid cancer among persons exposed to ^{131}I as children (Shakhtarin *et al.*, 2003; Cardis *et al.*, 2005). Conversely, prolonged stable iodine supplementation in the years after exposure may reduce this risk (Cardis *et al.*, 2005). Further studies are needed to replicate these findings.

The relative contributions of ^{131}I, short-lived isotopes of iodine, external exposures and long-lived nuclides were considered in one case–control study (Cardis *et al.*, 2005), which concluded that the observed increased risk of thyroid cancer after the Chernobyl accident appears to be mainly due to ^{131}I. Doses from other radiation types were low, however, and it is difficult to evaluate the carcinogenic potential of shorter lived isotopes of iodine.

Papillary cancer is the primary pathological type of thyroid cancer found in those exposed as children and adolescents to fallout from the Chernobyl accident. It does not appear that the biology of radiation-induced thyroid cancer is fundamentally different from that seen in a non-irradiated population. A slightly greater percentage of radiation-induced thyroid cancers appear to be papillary in nature (Williams *et al.*, 2004). Possible differences in the molecular biology of the tumours, particularly with regard to proto-oncogene *RET/PTC* rearrangements and *BRAF* mutations, are unclear at this time (Detours *et al.*, 2005; Powell *et al.*, 2005).

(ii) Exposures in utero and preconception

Data on exposure to the embryonic/fetal thyroid are rare, raising questions about use of ^{131}I in pregnant women. A total of seven cases of thyroid carcinoma were identified during 2003–06 in a cross-sectional thyroid screening study of children who were *in utero* at the time of the accident and whose mothers were part of a cohort with direct thyroid measurements in Ukraine. Of these, six cases were diagnosed among the 1494 children from contaminated areas, and one from the comparison group of 1088 children from less contaminated areas. Individual cumulative in-utero thyroid dose estimates were derived from estimated ^{131}I activity in the mothers' thyroid (mean 72 mGy; range 0–3230 mGy). The estimated excess odds ratio per grey for thyroid cancer was 11.66 (95%CI: < 0–1982; Hatch *et al.*, 2009).

Effects of in-utero and preconception exposure were also investigated in a cross-sectional screening survey of children from the Gomel region of Belarus living in five areas that were within 150 km of the Chernobyl nuclear power plant (Shibata *et al.*, 2001). One case of thyroid cancer was identified among 2409 children who were *in utero* at the time of the accident compared to 31 among 9720 children exposed in the first three years of their life. No cases were diagnosed among the 9472 children screened who were conceived in the three years following the accident.

(iii) Exposures in adults

Although the increased risk of thyroid cancer in those exposed in childhood and adolescence is well demonstrated, the effect of exposure on adults remains unclear. Increased incidence of thyroid cancer was reported among 60000 liquidators, 50000 evacuees, and 360000 residents of the most contaminated areas of Ukraine (Prysyazhnyuk *et al.*, 2007); among the latter, the increase appeared to be related to radioiodine fallout. An increased incidence of thyroid cancer was also reported in cohorts of liquidators from Belarus and the Russian Federation (Okeanov *et al.*, 1996; Ivanov *et al.*, 1997) compared to the general population of these countries and, more recently, based on small numbers of cases in a Baltic cohort of liquidators from Estonia and Latvia (Rahu *et al.*, 2006). [The Working Group noted that the possible effect of differential screening among liquidators and in regions with different levels of contamination (Cardis & Okeanov, 1996; UNSCEAR, 2000b) could, however, at least partially explain these observations.] Among residents of contaminated areas of the Russian Federation, no dose–response relationship was found for thyroid cancer following exposures in adulthood (Ivanov *et al.*, 2003).

(b) Other cancers

The highest organ-specific radiation doses from the Chernobyl accident were to the thyroid gland; exposure occurred primarily from ingestion of milk contaminated with radioactive iodines, particularly ^{131}I, and epidemiological studies of the effects of radioiodines after Chernobyl have therefore focused on the risk of thyroid diseases. No analytical study of other endpoints in relation to radioiodines was therefore available for review.

2.3.2 Other environmental exposure to radioiodines

(a) Cancer of the thyroid

Table 2.2 (available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-05-Table2.2.pdf) summarizes studies of thyroid cancer risk following exposure to radioiodines from fallout from atmospheric weapons testing, and from releases from the Hanford plant in Washington State in the USA.

In the Marshall Islands study (Takahashi *et al.*, 1999, 2001), two surrogate measures of radiation dose were derived for the subjects who were alive at the time of the BRAVO test. Associations were found between the risk of thyroid cancer and both of these measures. No association was found between estimated thyroid dose and risk of thyroid cancer in the Hanford study (Davis *et al.*, 2004). A statistically significant association was found between estimated radioiodine dose from the Nevada test site and risk of thyroid neoplasms in Utah, Nevada, and Arizona, (Lyon *et al.*, 2006), based on revised thyroid dose estimates and a detailed assessment of dosimetric uncertainties. Numbers of cases in each of the studies were small, however, compared to those in the aforementioned Chernobyl studies.

(b) Other cancers

As in the case of Chernobyl, the highest organ-specific radiation doses from the releases were to the thyroid gland. No analytical study of other end-points in relation to radioiodines was therefore available for review.

2.3.3 Medical exposures to ^{131}I

^{131}I is currently the treatment of choice for hyperthyroidism and thyroid cancer, and is used broadly for diagnostic investigations of thyroid diseases.

(a) Cancer of the thyroid

As indicated in Volume 78 of the *IARC Monographs* (IARC, 2001), several studies of the carcinogenic effect of radioiodine involved patients treated for hyperthyroidism (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100D/100D-05-Table2.3.pdf). Significantly increased risks of thyroid cancer were seen overall in some studies of patients treated for hyperthyroidism, based on small numbers of cases (Hall *et al.*, 1992; Ron *et al.*, 1998; Franklyn *et al.*, 1999). No study focused specifically on populations exposed to ^{131}I in childhood or adolescence for the treatment of hyperthyroidism; furthermore, there were very small numbers of subjects below the age of 20 years at diagnosis in the hyperthyroidism cohorts. In a review paper, however, Shore (1992) carried out an analysis of risk in those exposed below the age of 20 years in the Swedish and US studies. The total population was estimated to be 602 with an approximate average follow-up of 10 years and a mean dose to the thyroid of about 88 Gy. A total of two cases of thyroid cancer were reported, compared to about 0.1 expected. The estimated ERR/Gy was 0.3 (90%CI: 0.0–0.9) and the EAR was 0.1×10^{-4} PY/Gy (90%CI: 0.0–0.2).

The risk of thyroid cancer following diagnostic examination with ^{131}I was studied in a cohort of about 35000 patients below the age of 75 years (Holm, 1991). In a further follow-up of this cohort up to 1998, excess thyroid cancer risk was seen only for those who received previous external radiation therapy to the neck and those who were referred due to suspicion of thyroid tumours (Dickman *et al.*, 2003).

(b) Other cancers

The risk of any cancer following diagnostic examination with ^{131}I was also studied in a Swedish cohort of about 35000 patients below the age of 75 years (Holm, 1991). An increased risk of second cancers was observed 5–9 years after

examination (SIR, 1.07; 95%CI: 1.01–1.14, based on 964 cases).

Increases in the risk of tumours at other sites have been reported in populations of patients treated with ^{131}I for benign or malignant thyroid conditions.

In a US study, the incidence of leukaemia following treatment of hyperthyroidism did not differ between a group of 22000 patients treated with ^{131}I and those treated surgically (Saenger *et al.*, 1968), nor was it increased in a study of 10552 patients treated in Sweden during 1950–75 (Holm *et al.*, 1991) or in a study of 2793 patients treated during 1965–2002 in Finland (Metso *et al.*, 2007).

In the same study in Sweden, the SIR for all cancers was 1.06 (95%CI: 1.01–1.11) compared to the Swedish population (Holm *et al.*, 1991); it was 1.25 (95%CI: 1.08–1.46) in the Finnish study (Metso *et al.*, 2007).

In the Swedish study, significant increases were seen for cancers of the lung and kidney and, among 10-year survivors, for cancers of the stomach, kidney and brain. Only the risk for stomach cancer, however, increased with the level of administered ^{131}I dose, and this increase was not statistically significant; the estimated relative risk at 1 Gy for stomach cancer was 2.32, and the absolute risk was 9.6×10^{-4} PY/Gy (Holm *et al.*, 1991).

In the Finnish study, the incidence of stomach, kidney and breast cancer was increased among patients treated with radioiodines, and the relative risk increased with the level of radioiodines administered (Metso *et al.*, 2007).

In patients treated for thyroid cancer, no significantly increased risk of leukaemia or breast cancer was observed in a study of 834 patients from Sweden (Hall *et al.*, 1991), though increased incidences were observed for tumours of the salivary gland, genital organs, kidney and adrenal gland in women. These increases could not, however, be linked to high-dose ^{131}I exposures.

In combined analyses of data on 4225 thyroid cancer cases treated with ^{131}I in France, Italy and Sweden (Rubino *et al.*, 2003), increased risks of solid tumours, leukaemia, colorectal cancer and soft tissue and bone sarcoma were observed with increasing cumulative activity of ^{131}I administered. A significant association was also found between ^{131}I administration and the occurrence of bone and soft tissue, female genital organs, and salivary gland cancers, but not breast cancer. A marginally significant association was seen for tumours of the central nervous system (RR, 2.2; 95%CI: 0.9–5.7). For colorectal cancer, a role for cancer susceptibility in the carcinogenic response to radioiodine was suggested in a study that used familial aggregation as a proxy of inherited cancer susceptibility in a nested case–control study within the French cohort of thyroid cancer patients (Rubino *et al.*, 2005).

In a study of 875 patients from France, an overall increased risk of second primary malignancies was seen in women but not in men (Berthe *et al.*, 2004); the increased risk was related to cancer of the genitourinary tract and cancer of the kidney. Cumulative activity of ^{131}I was not, however, related to the risk.

In a study of 30278 thyroid cancer patients in the US, a significantly increased risk of second primary malignancies (in particular all cancers, leukaemia, stomach and prostate cancer) was seen for patients treated with radioisotopes (Brown *et al.*, 2008). Non-significant increases were seen for breast cancer and cancers of the central nervous system. The greatest risk of second malignancies was seen within 5 years of diagnosis, however, and no information about level of ^{131}I activity was available.

2.4 Synthesis

Relatively few epidemiological studies have assessed the carcinogenic effects of ^{3}H intakes in human populations; the typically low doses encountered in occupational and environmental

settings pose challenges for epidemiological studies of this radionuclide. The most detailed investigation of this question has involved UKAEA workers. These studies noted a significantly elevated relative risk of prostate cancer among workers with documented intake of ^{3}H that tended to increase in magnitude with duration of ^{3}H monitoring; this association diminished in magnitude in more recent calendar years of follow-up; however, ^{3}H doses were not quantified and there is potential for confounding by other occupational exposures.

The epidemiological literature provides consistent evidence of an elevated risk of leukaemia among patients treated with ^{32}P, and the study by Modan & Lilienfeld (1965) showed a significant association between ^{32}P treatment and the occurrence of acute leukaemia in *polycythaemia vera* patients. Modan & Lilienfeld (1965) also demonstrated a dose–response association between ^{32}P and leukaemia. Subsequent studies, although methodologically weaker for drawing inferences on specific effects of ^{32}P, support the observation of elevated rates of acute leukaemia among patients treated by ^{32}P relative to patients treated by phlebotomy (Parmentier, 2003; Finazzi *et al.*, 2005).

No new study was available to the working group that allows the evaluation of the possible carcinogenic effect of ^{137}Cs on its own. For studies of mixed exposures, see Section 2.1.4.

Based on the increased risk of solid cancers and of leukaemia among residents of the Techa River area, the working group considered that the mixture of external exposure and internal exposures predominantly to ^{90}Sr causes cancer in humans.

Since the previous *IARC Monograph*, the evidence relating risk of thyroid cancer and exposure to radioiodines in childhood and adolescents from the Chernobyl accident has increased substantially, with several carefully conducted analytical epidemiological studies with individual dose estimation. Increased risks are also suggested for exposure to radioiodines from fallout from the Nevada and Marshall Islands atmospheric weapons tests. Information from studies of radioiodines from fallout about effects on thyroid cancer of exposure in adults remains scarce. The effect of exposures to radioiodines from fallout on the risk of tumours other than the thyroid has not been studied adequately.

Information from studies of medically exposed cohorts has increased since the previous *IARC Monograph* (IARC, 2001). More recent studies of cohorts of patients treated with ^{131}I indicate an increased risk of cancer. Increases in the risk of cancers at a variety of sites, including breast, central nervous system, kidney, digestive tract, salivary gland, as well as bone and soft tissue sarcoma and leukaemia have been reported in several studies. These observations may be related to detection and/or surveillance bias, shared genetic or environmental risk factors, or, in the case of cancer survivors, to ^{131}I treatment.

To date, most studies lack detailed information on levels of administered ^{131}I. In the studies that did evaluate this, however, apparent activity-related increases were observed for tumours of the salivary gland and digestive tract, for leukaemia and for bone and soft tissue sarcoma, but not for breast cancer.

3. Cancer in Experimental Animals

3.1 Previous evaluation

All radionuclides that emit β-particles that have been adequately studied, have been shown to cause cancer in experimental animals.

Lifetime studies of the carcinogenic effects of pure and mixed β-particle-emitting radionuclides have been conducted in experimental animals of several species that differ greatly in features such as size, metabolic characteristics, and lifespan. The locations and types of tumours observed were influenced by several factors

including the form of the radionuclide, the route by which it was administered, the resulting metabolic and dosimetric patterns, the age, sex and health status of the animals, and the presence of other agents.

Because the penetration of β-particles is usually greater than that of α-particles, effects on tissues may be seen not only at the primary site of radionuclide deposition, like the skeleton, but also in nearby tissues like the nasal or oral mucosa.

Since the previous *IARC Monograph* (IARC, 2001), only one study has been been published on the carcinogenicity of β-particle-emitting radionuclides in experimental animals. Thus, the Working Group reviewed the studies in the previous *IARC Monograph* and incorporated the experimental animals studies on other β-particle-emitting radionuclides that were not considered in the previous *IARC Monograph*.

3.2 Pure β-particle-emitting radionuclides

3.2.1 Tritium

The carcinogenicity of ^{3}H administrated as tritiated water ($^{3}H_2O$) was tested in mice by intraperitoneal injection (Johnson *et al.*, 1995) or oral administration (Yamamoto *et al.*, 1998), and in rats by intraperitoneal injection (Gragtmans *et al.*, 1984) producing thymic lymphoma and myeloid leukeamia in mice and mammary tumours [tumour type not specified] in rats.

3.2.2 Phosphorus-32

^{32}P injected intraperitoneally as Na_3PO4 to mice increased the incidence of leukaemia (Holmberg *et al.*, 1964). In rats, intraperitoneal injection of ^{32}P in an unspecified form produced osteogenic sarcomas (Koletsky *et al.*, 1950).

3.2.3 Strontium-90

^{90}Sr produced bone and lymphoid tumours in mice after its intraperitoneal injection as $^{90}Sr(NO_3)_2$ (Nilsson *et al.*, 1980). It produced osteosarcomas in dogs after intravenous injection, haemangiosarcomas were also found in dogs following inhalation and ingestion at a soluble form (Gillett *et al.*, 1992) and miniature pigs fed strontium-90 in the diet (NCRP, 1991).

3.2.4 Yttrium-90 and Yttrium-91

^{90}Y inhaled in an insoluble form produced lung cancers in dogs (Boecker *et al.*, 1994). ^{91}Y produced carcinomas and adenocarcinomas, lung, liver carcinomas and bone-associated nasal and oral mucosa tumours (squamous cell carcinomas and malignant melanoma) in dogs that inhaled a soluble form $^{91}YCl_3$ (Muggenburg *et al.*, 1998), and lung cancers in dogs that inhaled an insoluble form of $^{91}YCl_3$ (Boecker *et al.*, 1994).

3.2.5 Promethium-147

^{147}Pm caused lung adenomas, adenocarcinomas and epidermoid carcinomas tumours in Syrian hamsters injected intravenously with insoluble particles (Anderson *et al.*, 1979), and lung haemangiosarcomas and squamous cell carcinomas in rats exposed by inhalation (Herbert *et al.*, 1987, 1988).

3.2.6 Lutetium-177 and Samarium-153

Müller *et al.* (1980) studied the lifespan biological effects of two short-lived β-emitting radionuclides, ^{177}Lu (6.7 days half-life) and ^{153}Sm (47 hours half-life), injected intraperitoneally into weanling groups of 50 female NMRI mice 4 weeks of age. Both of these radionuclides are used in diagnostic and therapeutic nuclear medicine. Statistically significant incidences 6/48 (12.5%), 18/51 (35.5), 18/48 (37.5%) of osteosarcomas were noted in the mice injected with ^{177}Lu at injected

doses of 185 MBq/kg, 370 MBq/kg and 740 MBq/kg, respectively, compared to 0/50 animals in the control group. Animals injected with the highest dose (1480 MBq/kg) suffered severe damage to their incisors, a phenomenon that was also noted with ^{32}P (Bauer *et al.*, 1957). Consequently, these animals could not eat and were killed before they could develop bone cancer. Osteosarcomas from the short-lived ^{177}Lu occurred in the same dose range as those observed for the long-lived bone-seeking radionuclide, ^{90}Sr, i.e. 20–80 Gy. The lifespan study with intraperitoneally injected ^{153}Sm did not produce any osteosarcomas. This was evidently due to the use of a significant quantity of stable Sm carrier in the injection solution. Based on an observed significant shift of deposition of ^{153}Sm from bone to liver, compared to that for ^{177}Lu, it was concluded that the addition of 2 mg/kg Sm carrier resulted in the creation of colloidal species, which were taken up preferentially in organs rich in reticuloendothelial elements like the liver and spleen. As a result, severe degenerative changes in the liver were produced, but without liver cancer (Müller *et al.*, 1980).

3.3 Mixed β-particle emitting radionuclides

3.3.1 Calcium-45

Priest *et al.* (2006) exposed four groups of 160 female CBA/Ca mice by inhalation (nose-only) at four dose levels (0.5 Gy to about 5 Gy) to β particles from ^{45}Ca-labelled fused aluminosilicate particles (AFP) or to carrier AFP (400 mice). This was to study the relative ability of β particles in inducing lung cancer when given in inhaled amounts that would result in relatively equivalent absorbed doses to the lung, in producing lung cancer (i.e. RBE study). The target initial alveolar deposits (IADs) for the radionuclide were 0.8, 4.8, 8.8 and 12.8 kBq. Another group of 120 mice inhaled no AFP and were designated as untreated controls. The incidence of mice with malignant lung tumours after inhalation of carrier control AFP was 105/371 (28.3%). This incidence was not significantly different from the incidence of untreated mice with spontaneous lung tumours 36/124 (29%). A consistently higher number of mice with malignant lung tumours was observed in all of the ^{45}Ca-AFP-exposed groups (38/114, 33.3%; 33/109, 30.0%; 44/112, 39.3%; 53/109, 48.6%) compared with the carrier control and untreated control groups. This difference reached significance ($P < 0.05$ to $P < 0.001$) for all groups except for those that received the two lowest ^{45}Ca-AFP doses.

3.3.2 Iodine-131

^{131}I given by intraperitoneal injection to mice and rats produced thyroid adenocarcinomas, alveolar, follicular, and papillary carcinomas (Lindsay *et al.*, 1957; Walinder, 1972; Lee *et al.*, 1982).

3.3.3 Caesium-137

^{137}Cs produced malignant neoplasms (neurofibrosarcomas, haemangiosarcomas, carcinomas and cholangiocarcinomas) in the liver, biliary system, endocrine system (thyroid adrenal and pituitary glands), urinary system haemangiosarcomas and neoplasms in the renal haematopoietic system, genital system, and the respiratory system after intravenous injection to dogs (Nikula *et al.*, 1995, 1996).

3.3.4 Cerium-144

^{144}Ce inhaled in an insoluble form ($^{144}CeO_2$) produced lung adenomas, adenocarcinomas and squamous cell carcinomas in mice, rats, Syrian hamsters and dogs (Lundgren *et al.*, 1980 a, b, 1982, 1992a, b, 1996; Hahn & Lundgren, 1992), and lymph nodes and heart haemangiosarcomas in dogs (Hahn *et al.*, 1999). Dogs that inhaled a soluble form of ^{144}Ce ($^{144}CeCl_3$) developed lung,

liver, bone, oral and nasal mucosal, and haematopoietic neoplasms (Hahn *et al.*, 1995, 1997).

3.3.5 Radium-228

^{228}Ra may be considered a mixed β-particle emitter in 2-year carcinogenicity bioassays. ^{228}Ra produced osteosarcomas in dogs after intravenous injection (Mays *et al.*, 1987; Lloyd *et al.*, 1997).

3.4 Synthesis

A small number of studies on the carcinogenic effects of β-emitting radionuclides in experimental animals have been analysed or reanalysed since the previous *IARC Monograph* (IARC, 2001). These include results from studies on exposure to ^{45}Ca, ^{153}Sm, ^{177}Lu by intravenous injection and inhalation in mice and rats. The data from these studies support and confirm the Working Group's conclusions that all of the studied β-emitting radionuclides are carcinogenic (IARC, 2001). Because the patterns of radiation dose for these β-emitters are often non-uniform and specific to different tissues and organs, the site-specific cancer incidences vary based on the radionuclide, its physicochemical form, and route of administration.

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 exposure during childhood and adolescence to short-lived radioisotopes of iodine, including iodine-131. Exposure during childhood and adolescence to short-lived radioisotopes of iodine, including iodine-131, causes cancer of the thyroid. Also, positive associations have been observed between exposure to iodine-131 and cancer of the digestive tract and salivary gland, leukaemia, and bone and soft tissue sarcoma.

There is *sufficient evidence* in humans for the carcinogenicity of therapeutic administration of phosphorus-32, as phosphate. Therapeutic administration of phosphorus-32, as phosphate, causes acute leukaemia in patients with *polycythaemia vera*.

There is *sufficient evidence* in humans for the carcinogenicity of external exposure and internal exposure to fission products, including strontium-90. External exposure and internal exposure to fission products, including strontium-90, causes solid cancers and leukaemia.

There is *limited evidence* in humans for the carcinogenicity of strontium-90. A positive association has been observed between exposure to strontium-90 and leukaemia.

There is *inadequate evidence* in humans for the carcinogenicity of hydrogen-3.

There is *inadequate evidence* in humans for the carcinogenicity of caesium-137 alone or in combination with external radiation.

There is *sufficient evidence* in experimental animals for the carcinogenicity of the following β-emitting radionuclides: ^{3}H, ^{32}P, ^{90}Sr, ^{90}Y, ^{91}Y, ^{131}I, ^{137}Cs, ^{144}Ce, ^{147}Pm, ^{228}Ra.

There is *limited evidence* in experimental animals for the carcinogenicity of calcium-45 and Lutetium-177.

The radionuclide ^{228}Ra may be considered a mixed β-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-radiation predominate in long-term human exposure.

Short-lived radioisotopes of iodine, including Iodine-131 (^{131}I), are *carcinogenic to humans (Group 1).*

Phorphorus-32 (^{32}P), as phosphate, is *carcinogenic to humans (Group 1)*.

Mixtures of fission products are *carcinogenic to humans (Group 1)*.

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

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

- β-Particles emitted by radionuclides, irrespective of their source, produce similar patterns of secondary ionizations and the same type of localized damage to biological molecules, including to DNA. These effects include DNA double strand breaks, chromosomal aberrations, gene mutations and cell transformation.
- All radionuclides that emit β-particles and that have been adequately studied, have been shown to cause cancer in humans and in experimental animals. This includes hydrogen-3, which produces β-particles of very low energy, but for which there is nonetheless *sufficient evidence* of carcinogenicity in experimental animals.
- β-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 β -particles emitted during the decay of different radionuclides produce the same types of non-neoplastic effects and cancers.

All types of ionizing radiation are *carcinogenic to humans (Group 1)*.

In making this overall evaluation, the WG considered:

- All types of ionising radiation, even the neutron particle, transfer their energy to biological material as either divided or in clusters of ionization and excitation events, primarily through a free-electron-mediated mechanism.
- In cells, energy deposition from all types of ionizing radiation results in a wide variety of molecular damage; in DNA this includes base damage and single- and double-strand breaks, some of which may be clustered and form complex lesions. Subsequent processing of these lesions may lead to chromosomal aberrations and mutations.
- Much evidence points to damage to DNA being of primary importance in the biological outcome of exposure to ionising radiation.

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