5. Summary of Data Reported and Evaluation

5.1 Exposure data

The radionuclides considered in this monograph belong to two broad categories, those that emit α-particles (helium nuclei) and those that emit β-particles (electrons) during their primary radioactive decay. The α- and β-emitting radionuclides can be further characterized as 'pure' and 'mixed' emitters, primarily on the basis of the emissions of their decay products. Pure emitters in the strict sense, i.e. radionuclides that emit one type of radiation and have a stable isotope as their decay products, are rare, and they are seldom encountered as such in practical situations of human exposure. The predominant type of radiation released by mixed emitters during long-term internal exposure is calculated from the energy contributed by the various types of emission throughout the decay chain, integrated over an assumed period of 50 years after initial exposure. For all practical purposes, a decay product with a very long half-life may be considered to be the end of the decay chain, because its energy contribution and that of the decay products beyond it will be negligible. The overall biological consequences of exposure to mixed emitters result from the combined effects of their emissions and those of their decay products. Apart from α- and β-particles, these emissions may involve γ-radiation, X-rays and secondary electrons. In some cases, however, the overall mixture of emissions from a radionuclide and its decay products may be dominated, in terms of energy contribution, by one type of radiation, so that the radiobiological effect may be considered to be caused by this radiation alone.

Radionuclides that undergo radioactive decay processes which do not primarily involve emission of α- or β-particles are not considered in detail in this monograph. Examples are iron-55 and gallium-67, both of which decay through electron capture.

For the purposes of this monograph, 'internally deposited' refers to radionuclides in dispersed forms, e.g., dusts, suspensions, solutions or gases, that enter the body by inhalation, ingestion, some form of injection or, in some cases, by percutaneous absorption. Not considered in this monograph are radionuclides that enter tissues within removable objects, such as radioactive beads, pellets or needles, which may be implanted surgically for therapeutic purposes, or those that enter the body accidentally, in the form of other kinds of radioactive fragments.

The doses of radiation to organs and tissues in the body arising from intake of natural and man-made radionuclides are variable and depend on many factors, including geographical location and occupation. The major sources arise from the inhalation of radon-222; from the deposition of long-lived primordial isotopes of cosmic origin, namely

potassium-40, thorium-232 and uranium isotopes; from the deposition of shorter-lived decay products of primordial radionuclides, principally lead-210, polonium-210 and radium-226; and from anthropogenic radionuclides released into the environment, including strontium-90, ruthenium-106, iodine-131, caesium-137, plutonium isotopes and americium-241. Potential exposure of lesser importance may occur after accidental intake from miscellaneous radioactive devices such as thorium-232 gas-lantern mantles, americium-241-containing fire detectors and polonium-210-containing anti-static devices.

In addition, as a consequence of their employment, workers may be exposed to and absorb radionuclides that occur in the nuclear fuel cycle; in radiopharmaceuticals such as technetium-99m, iodine-131, phosphorus-32 and strontium-90; in radiolabelled compounds (mostly hydrogen-3 and carbon-14-labelled organic compounds); and a variety of miscellaneous sources. Patients may also take in radionuclides during diagnostic medical procedures or for the treatment of severe diseases — principally cancer and diseases of the skeletal system — such as with iodine-131 and radium-224. Finally, tobacco smoking may result in intakes of the volatile radionuclides lead-210 and polonium-210.

For most members of the public, the dose of ionizing radiation received from inhaled and tissue-deposited radionuclides is predominantly from inhalation of naturally occurring radon-222. This accounts for about one-half of the 2.4 mSv/year which is the average total background effective dose of radiation received from all sources, including external ionizing electromagnetic radiation. However, in some geological areas, the fraction of the total effective dose received from radon-222 may easily exceed 80% of the annual average background effective dose.

Similarly, exposure to thorium-232, uranium isotopes and their shorter-lived decay products is variable and depends principally upon their concentration in soils. Such radionuclides may enter the body as the result of inhalation of resuspended soil particles containing these elements and/or their presence in food and water. However, the effective dose received from these sources is smaller than that received from radon-222. In contrast, the body content of the radioisotope potassium-40, which comprises 0.2% of total potassium, is maintained at a constant level as a result of the metabolic processes that control the tissue concentration of this element in the body. Again, the contribution to the total effective dose from potassium-40 is small, averaging 0.175 mSv/year.

Nuclear explosions, nuclear fuel reprocessing, nuclear-generated electricity and accidents at nuclear facilities all result in increased exposure of workers and of the general population to radionuclides. For the general population, the body content of anthropogenic nuclides from such sources is usually small. The effective radiation dose received from global fall-out, i.e. from nuclear fission products and fuel components (principally plutonium-239, -240 and -241 and americium-241) released into the atmosphere by the explosion of nuclear devices, accounts for only 0.01 mSv of the contemporary annual background effective dose of 2.4 mSv. This dose is uniform

within populations in the two hemispheres — a result of the dispersion of most fall-out throughout the atmosphere of the northern hemisphere and its subsequent but significantly delayed transfer at a lower level to the southern hemisphere or *vice versa*.

Intakes of radionuclides originating from the nuclear industry, released either accidentally or deliberately, e.g. krypton-85, are also normally low but can be high under some circumstances. For instance, intake that is much higher than normal may occur among persons living close to the sites of releases of nuclear fuel reprocessing effluents, e.g. in West Cumbria, United Kingdom, or the Techa River in the Russian Federation, since the wastes may contain fission products such as caesium-137 and strontium-90 and fuel-derived components such as plutonium-239, plutonium-241 and americium-241. Reactor accidents such as those at Chernobyl and Windscale resulted in the release of more volatile fission products into the environment, including iodine and caesium isotopes, and the exposed populations had much higher than normal intakes of these radionuclides.

Similarly, some local populations have been exposed non-occupationally to radionuclides released during nuclear weapons testing, for example, in St George, Utah (USA), on Pacific islands within the fall-out plume from testing at Bikini atoll and in Sarzhal, Kazakhstan, close to the Semipalatinsk nuclear test site of the former USSR. Under these conditions, the intake of radionuclides reflects the spectrum of fission products released by the device, except that the delay between detonation of the device and exposure must be very short if the intake of short-lived isotopes, such as those of iodine, is to be significant. Radionuclides originating from nuclear fuel wastes may be taken in after deliberate releases and accidents at fuel reprocessing facilities, such as occurred at Mayak in the southern Urals. Normal operation of nuclear energy power plants results in little radionuclide intake by members of the public, but they may be exposed to radionuclides of primordial origin in the fly ash released by conventional thermal power plants.

Workers involved in the manufacture and application of radionuclides, including those for medical purposes, are also exposed. Such exposure is usually regulated by local procedures designed to limit occupational exposure of classified workers to a maximum of 20 mSv in any one year or of unclassified workers to the lower limit of 1 mSv/year. These are internationally recognized standards recommended by the International Commission on Radiological Protection. However, in the past, other national and international standards have applied that have resulted in higher permitted intake of radionuclides, and, in addition, accidents have resulted in intakes that exceed these limits.

In the uranium–plutonium fuel cycle, the most significant radionuclides with respect to occupational exposure are strontium-90, caesium-134, caesium-137, curium-242, americium-241 and plutonium isotopes. With other fuel types, e.g. thorium fuels, other radionuclides are also important, particularly thorium-238, protactinium-231 and uranium-239. Currently, however, use of this type of fuel cycle is low. In western Europe and the USA, studies have shown that the plutonium body burdens seldom

exceed 1 kBq; in the countries of the former USSR, e.g. in the Mayak nuclear complex, however, many workers have plutonium body burdens that exceed this amount.

5.2 Human carcinogenicity data

Radon

Twelve cohort studies of underground miners exposed to high concentrations of radon-222 and its short-lived decay products in air have been carried out in several countries. Additionally, the data from 11 of these studies were pooled and analysed. Each individual study and the pooled analysis showed clear evidence of an increased risk for lung cancer associated with exposure to radon. In none of the studies was convincing evidence found for an increase in the risk for death from cancer other than lung cancer.

Thirteen case–control studies addressed the association between lung cancer and residential exposure to radon. A meta-analysis of eight of these studies and subsequent studies found an association between exposure to radon and lung cancer. The risk estimates from studies of residential exposure are consistent with those predicted from the studies of underground miners.

Radium

The studies of cancer risk among radium watch-dial painters in the USA, some of whom ingested radium-226, often in combination with radium-228, 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. 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. It is also clear that excess risk for carcinomas of the paranasal sinuses and mastoid process is associated with internally deposited radium-226, but probably not radium-228. An association between exposure to α-particles from internally deposited radium-226 and radium-228 and other cancers has not been well established.

Bone sarcomas were the major late effect among patients with tuberculosis, ankylosing spondylitis and other diseases who were treated with high doses of radium-224 (mean bone surface dose, 30 Gy). Significant increases in the incidences of cancers of the breast, kidney, liver, urinary system, thyroid and soft tissues were also observed. The number of cases of leukaemia was greater than expected, but, after allowance for a minimum delay of two years after exposure, the increase was not statistically significant. Among ankylosing spondylitis patients treated with lower doses of radium-224 (mean bone surface dose, 5 Gy), several tumours originating in the bone were observed, and there was an excess risk for leukaemia. There is no reason to doubt the

radiogenic origin of the bone tumours in patients treated with radium-224. The reasons for the increased incidences of other cancers are at present unclear.

Thorium

Occupational exposure to thorium by inhalation of fine particles containing thorium and its decay products occurred in thorium refineries and in mines of monazite and rare-earth ores. Two epidemiological studies, in China and the USA, cover more than 6000 exposed workers. Although a high radiation burden could be demonstrated, especially in lung tissue, the results of the studies are not conclusive in showing an elevated risk for lung cancer due exclusively to the inhaled radioactive substances. Large differences in smoking habits and the effects of dust on the broncho-epithelial system must also be considered.

Stabilized thorium-232 dioxide (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. Cohort studies of almost 10 000 patients given Thorotrast and 10 000 controls in Denmark, Germany, Japan, Portugal and Sweden have demonstrated significantly increased risks (by 36–129 times) for primary liver cancer (approximately one-third being haemangiosarcomas), which are significantly correlated with the volume of Thorotrast injected. The incidence of and mortality from liver cirrhosis were also significantly increased in all studies (by 6–13 times). These studies have also shown a significantly increased risk (by 11–20 times) for leukaemia excluding chronic lymphocytic leukaemia. Increased risks for cancers at other sites were reported in some studies but not consistently. Consistent increases have not been found for lung cancer, although patients given Thorotrast exhale high concentrations of radon-220 (thoron).

Plutonium

At the Mayak plutonium production plant in the Russian Federation, exposure to plutonium (chiefly plutonium-239) was substantial, large numbers of workers having estimated body burdens greater than 3 kBq. Some workers had such heavy exposure to plutonium that they developed pulmonary sclerosis, a condition reported previously only in animals given very large doses of this element. Increased risks for cancers of the lung, liver (including haemangiosarcoma) and bone (predominantly osteosarcoma) have been observed among these workers. Dose–response relationships have been 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 have not been studied. Very few workers in the United Kingdom and the USA were estimated to have plutonium body burdens greater than 1 kBq, and no health risks were convincingly linked to this low exposure.

Uranium

Some studies of workers in uranium processing have shown an increased mortality rate from lung cancer, although the finding is not consistent. The doses to the lung were relatively low. The mortality rates from other site-specific cancers were increased in some studies, but the small numbers of cases and lack of consistency among these findings make them difficult to interpret. The studies of workers exposed to uranium are hampered by difficulty in measuring the dose of radiation, potential concomitant exposure to chemicals, possible effects of age at the time of exposure, the 'healthy worker effect' and confounding by smoking.

Polonium

The epidemiological studies of nuclear industry workers exposed to polonium-210 are inadequate to allow a conclusion about cancer risk. In only one study were data available to analyse dose–response relationships, but the cohort was small, and no significant trends were identified in the rates of death from all causes, all cancers or specific cancers.

Iodine

After the accident at the Chernobyl nuclear reactor in the Ukraine in 1986, substantial increases in the incidence of thyroid cancer were observed among persons exposed during childhood in the regions most heavily contaminated with iodine isotopes (iodine-131 and short-lived isotopes in varying combinations) in Belarus and the Ukraine and — to a lesser extent — the Russian Federation. The evidence that this increase is related to exposure to iodine isotopes is indirect, yet it is very strong.

Geographical correlation studies in Belarus, the Russian Federation and the Ukraine have shown strong correlations between the presumed dose to the thyroid and the incidence of thyroid cancer among persons exposed during childhood or *in utero*, and most of the tumours to date have appeared in children. A significant dose–response relationship was observed in a case–control study of thyroid cancer in children carried out in Belarus. Overall, the number of thyroid cancers in individuals exposed during childhood, particularly in the severely contaminated areas of the three countries, is considerably greater than that expected on the basis of previous information on the effects of iatrogenic exposure of adults to radioiodine.

In a cohort study of persons exposed to iodine isotopes in fall-out from nuclear weapons testing in southwestern USA, a significant dose-related increase in the risk for benign and malignant thyroid tumours combined was seen; the increase was not, however, significant for malignant thyroid tumours alone. In the Marshall Islands, increases in the incidences of thyroid cancer and thyroid nodules were observed among persons exposed during childhood to iodine-131, other short-lived isotopes of iodine and external radiation from nuclear weapons testing.

In contrast, no appreciable increase in the risk for radiation-related thyroid cancer was observed in several comprehensive follow-up studies of populations who had received diagnostic or therapeutic exposure to iodine-131 for thyroidal conditions. This finding does not, however, contradict the results of the follow-up of persons exposed as a result of the Chernobyl accident or in the Marshall Islands, as the published studies of diagnostic exposures included very few exposed children and therefore do not provide information about the risk of exposures during childhood. Studies of persons exposed to external radiation also suggest that the risk for thyroid cancer is restricted to exposure during childhood.

The risk for leukaemia after exposure to iodine-131 for medical purposes has been examined in a number of studies. No exposure-related increase has been seen. Furthermore, no increase in the incidence of leukaemia has been reported among persons exposed to radioiodines as a result of the Chernobyl accident.

Phosphorus

The risk for acute leukaemia is clearly increased in patients with polycythaemia vera who were treated with phosphorus-32 in comparison with those given treatments that did not involve irradiation. However, as polycythaemia vera is a clonal malignancy of the pluripotent haematological stem cells, patients with this disease may be more sensitive to the leukaemogenic effects of irradiation than the general population.

Combined exposures (external and internal)

Persons exposed during weapons testing received mainly radioactive iodine, and studies of these populations are discussed above.

In a study of a population in the Russian Federation exposed to a mixture of internally deposited radionuclides (predominantly strontium-90) and external radiation (see IARC, 2000), a dose-related increase in the rates of mortality from solid tumours and leukaemia was observed.

Other radionuclides

Humans have been exposed to a large number of other radionuclides, including caesium-134, caesium-137, hydrogen-3 and carbon-14. There are, however, few or no epidemiological data, and their effects on humans could not be quantified.

5.3 Animal carcinogenicity data

In the summaries of the studies of carcinogenicity in animals exposed to internally deposited radionuclides, a distinction was made between pure and mixed α- and β-emitters, according to the definitions given in the General Remarks. In evaluating the effects of mixed emitters in animals, it is important to discern which type of emitted

radiation predominates over the average lifespan of the animals, which — especially for rodents — is often shorter than the decay half-life of some radionuclides. Two radionuclides considered in this monograph are classified differently as effective α- or β-emitters for humans and for short-lived experimental animals. Thus, the effects of thorium-232 in two-year bioassays in rodents can be ascribed to pure α-radiation, owing to the long half-life (5.75 years) of its primary decay product radium-228. When humans are exposed to thorium-232, sometimes over several decades, the radionuclide can be considered a mixed α-emitter, exposing tissues predominantly to α-radiation and small amounts of β- and γ-radiation. In two-year bioassays in rodents, radium-228 can be considered a mixed β-emitter, exposing tissues to β- and γ-radiation, owing to the 1.9-year half-life (comparable to the animals' lifespan) of its second decay product, thorium-228. When humans are exposed to radium-228, sometimes over several decades, the cumulative energy spectrum is dominated by α-radiation from radionuclides further down the decay chain.

α-Particle-emitting radionuclides

Lifetime studies of the carcinogenicity of pure and mixed α-particle-emitting radionuclides have been conducted in experimental animals of a number of species and strains that differ greatly in features such as size, metabolic characteristics and lifespan. The locations and types of tumours observed were influenced by factors including species, the form and route of administration, the resulting metabolic and dose patterns and the age and health status of the animals. α-Particles have a short range of penetration in biological tissues, and tumours developed at the sites of radionuclide deposition.

The carcinogenicity of radon isotopes in animals was evaluated previously (IARC, 1988).

Lung tumours were observed in hamsters given polonium-210 by intratracheal instillation. Radium-224 given parenterally to mice and dogs resulted in bone tumours; haematopoietic tumours were also observed in mice. Radium-226 administered to mice, rabbits and dogs by intraperitoneal or intravenous injection caused bone cancers. Skeletal cancers occurred in mice given thorium-227 by parenteral injection and in dogs given thorium-228 by intravenous injection. Rats and mice exposed to thorium-230 and thorium-232 in a colloidal form and hamsters given colloidal thorium-232 as Thorotrast developed liver cancers.

Lung cancers were observed in hamsters exposed to plutonium-238 by inhalation. Lung, liver and bone cancers were observed in dogs exposed by inhalation to plutonium-238 or plutonium-239; the plutonium preparations used in many studies also contained small amounts of plutonium-240. In mice, hamsters and dogs exposed to plutonium-239 by parenteral administration, bone and liver cancers were observed; haematopoietic cancers were also observed in mice. Lung cancers were observed in rats exposed by inhalation to uranium ore dust. Mice injected intraperitoneally with

americium-241 developed liver, bone and haematopoietic cancers. In rats and dogs exposed to americium-241 by intravenous injection and in dogs exposed by inhalation, bone and liver cancers were observed. Skeletal cancers were observed in mice given californium-249 or californium-252 intraperitoneally and in dogs treated intravenously. Skeletal cancers were also observed in rats exposed by intravenous injection to curium-242 and curium-244 and lung and liver cancers in rats exposed by inhalation.

β-Particle-emitting radionuclides

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

The carcinogenicity of hydrogen-3 was tested in mice by intraperitoneal injection or oral administration and in rats by intraperitoneal injection, producing tumours of the haematopoietic system in mice and mammary tumours in rats. Phosphorus-32 injected intraperitoneally to mice increased the incidence of leukaemia. In rats, intraperitoneal injection of phosphorus-32 produced osteogenic sarcomas. Strontium-90 produced bone and lymphoid tumours in mice after its intraperitoneal injection. It produced bone tumours in dogs after intravenous injection or inhalation of a soluble form. Haematopoietic neoplasms and bone cancers were also found in dogs and miniature pigs fed strontium-90 in the diet. Yttrium-90 inhaled in an insoluble form produced lung cancers in dogs. Yttrium-91 produced lung, liver and bone tumours in dogs that inhaled a soluble form and lung cancers in dogs that inhaled an insoluble form. Promethium-147 caused lung tumours in Syrian hamsters injected intravenously with insoluble particles and in rats exposed by inhalation.

Iodine-131 given by intraperitoneal injection to mice and rats produced thyroid cancers. Caesium-137 produced liver, haematopoietic and other neoplasms after intravenous injection to dogs. Cerium-144 inhaled in an insoluble form produced lung tumours in mice, rats, Syrian hamsters and dogs. Dogs that inhaled a soluble form of cerium-144 developed lung, liver, bone and haematopoietic neoplasms. Radium-228 produced bone tumours in dogs after its intravenous injection.

Perinatal carcinogenesis

Some radionuclides have been tested for their carcinogenicity to offspring when given during the prenatal and/or neonatal period. The temporal distribution and spatial localization of the dose affect the response. Moreover, the dose rates and cumulative doses of radiation to the embryo or fetus are affected by the stage of development at the time of exposure.

Dose-dependent increases in tumour incidence and shorter times to tumour appearance have been found after perinatal exposure, but the tumour incidences may be decreased, especially at high doses, due to death, inhibition of development of target tissues or endocrine malfunction. Age-related differences in the predominant tumour types and/or sites of tumour development are due to the existence of radionuclide-specific target organs or tissues, dosimetric factors and different sensitivity at various stages of tissue differentiation and development.

Plutonium-238 and plutonium-239 caused bone tumours in rats exposed prenatally or neonatally. The sensitivity of these animals per unit dose of radiation was greater than that of adults. Tumours were found frequently in the skull, which received the highest dose of radiation as a result of its proportionately greater size during fetal and neonatal life.

Americium-241 also produced skeletal tumours in mice and rats exposed perinatally, and there is some evidence that it is more potent than plutonium.

Increased incidences of ovarian or reticuloendothelial tumours were found in the offspring of mice exposed to water labelled with hydrogen-3 during gestation in two separate experiments. A slight increase in the incidence of ovarian tumours and a decrease in the incidence of mammary tumours were found in the offspring of exposed rats. Prenatal or neonatal exposure of mice to thymidine labelled with hydrogen-3 caused increased incidences of miscellaneous tumours not ordinarily found in the strains of mice tested, and commonly occurring tumours were seen earlier or at increased incidence.

In one study, the offspring of rats exposed prenatally to phosphorus-32 developed neurogenic tumours. In another study, the time to appearance of bone tumours in postnatal life was reduced, although the overall incidence was not increased. In mice, the incidence of leukaemia was increased in female offspring.

Strontium-90 was carcinogenic to the offspring of mice, increasing the incidence of ovarian tumours. In the offspring of rats, increased incidences of pituitary tumours and lymphoid tumours of the thymus were observed.

Although bone tumours were produced by cerium-144 in rats exposed as weanlings, no bone tumours were seen in rats exposed at birth.

Mice and rats have shown greater sensitivity to thyroid tumour induction by iodine-131 after prenatal and neonatal exposure than after exposure as adults.

Paternal exposure

In one study, irradiation of male mice with α-particles from plutonium-239 produced genetically transmissible damage, manifested as an increased susceptibility of their offspring to subsequent exposure to known carcinogens.

5.4 Other relevant data

Absorption, distribution, metabolism and excretion

The distribution of dose from radionuclides deposited within the body depends on the amount and route of intake, the physicochemical form and types of radiation emitted, the physical half-life of the isotope, the organs and tissues in which the radionuclide is retained and the duration of retention. Internally deposited radionuclides, particularly those that emit poorly penetrating α- and low-energy β-particles, may preferentially irradiate specific tissues and specific cells within tissues. Depending on the radioactive half-life and the duration of retention in body tissues, a dose may be delivered for a very short period or over the lifetime of the individual.

Data on the behaviour of radionuclides in the body are used with information on the geometric arrangements of organs and tissues within the human body to construct models for calculating organ and tissue doses. These models take account of the dose to both those tissues that contain the radionuclide and those that do not. The location of sensitive cells within tissues is also taken into account (e.g. in bronchial airways and adjacent to bone surfaces). The reliability of dose estimates depends on the quality of the data on which the assumptions of the model are based.

The estimated doses to organs and tissues from different radionuclides, expressed as Gy/Bq, can vary by many orders of magnitude. For example, the dose received by adults exposed to hydrogen-3-labelled water, either by ingestion or inhalation of vapour, has been calculated to be 1.8×10^{-11} Gy/Bq, with uniform doses to all tissues, whereas the dose near bone surfaces after inhalation of plutonium-239 or americium-241 has been calculated to be 8×10^{-5} Gy/Bq. While the dose from hydrogen-3 is delivered over a period of weeks, plutonium-239 and americium-241, which have longer biological half-lives, continue to deliver their dose throughout the lifetime of the exposed person.

The estimated tissue doses of radionuclides can be used to predict the risk for induction of various cancers under particular conditions of exposure and to compare the effects of different radionuclides.

Toxic effects

Radiation from internally deposited α- and β-particle emitters produces dose-dependent pathological alterations in tissues over a wide range of cumulative tissue doses. Most authors have suggested that these effects are qualitatively similar to those produced by external irradiation with X-rays or γ-rays. The most important of these

changes result from deterministic effects, including cell death, vascular damage and tissue fibrosis. Information on the relative biological effectiveness of various radiation types is complicated by considerations of chemical toxicity, such as that of neptunium-237, and by differences in the deposition patterns of different radionuclides in the tissues studied. Moreover, even when radionuclides are similarly distributed, e.g. strontium-90 and radium-224, the spatial and temporal distribution of dose may differ substantially, such that any comparisons made are at best difficult and at worst meaningless. Most of the evidence suggests that α-particle emitters cause more tissue damage than external γ-radiation per unit absorbed dose.

The available evidence suggests that tissue damage occurs over a very wide range of tissue doses and probably always occurs after α-irradiation — a consequence of the cell killing by this type of radiation. Some authors have suggested that the cancer induction process is linked to the onset of deterministic effects.

Reproductive and developmental effects

A reasonably clear, quantitative picture is available of the developmental toxicity of prenatal and neonatal exposure to incorporated radionuclides. The effects include decreased prenatal or postnatal growth, reduced reproductive capacity, malformations and prenatal or postnatal death or life shortening. Some of the data allow direct or indirect comparisons with effects in adults and analysis of relationships to administered activity, radiation dose and the spatial and temporal distributions of radionuclides. Only inferential information is available on the effectiveness of particulate radiations relative to that of external photons or neutrons.

Heavy exposure of animals to radon-222 has been shown to cause prenatal haemorrhage and fetal death. Reduced fertility has been demonstrated in women with high body burdens of radium after occupational exposure, but this effect has not been demonstrated in experimental animals. Studies of americium and isotopes of plutonium in experimental animals have shown adverse effects on prenatal mortality, haematopoiesis and postnatal growth and life-span. Continuous exposure of pregnant animals to hydrogen-3-labelled water or thymidine resulted in prenatal death, decreased birth weights, retarded postnatal growth, effects on gonadal development, altered brain histogenesis and behavioural deficits. Studies in which preimplantation embryos were exposed to hydrogen-3 *in vitro* consistently showed greater effects on development when the radionuclide was incorporated into thymidine rather than into water. Exposure of animals to phosphorus-32 *in utero* led to prenatal death, reduced growth, malformations and gonadal and pituitary lesions. Exposure of animals to strontium-90 *in utero* had deleterious effects on fetal and neonatal ovaries and a lesser effect on the development of the testis. Fetal exposure to iodine-131 affected the development of the thyroid in humans and animals to a greater extent than postnatal exposure.

Genetic and related effects

All ionizing radiations can disrupt molecules and produce many types of DNA damage, ranging from isolated base damage or single-strand breaks to simple double-strand breaks and more complex DNA alterations involving clustered damage sites with multiple breaks and/or base changes. Clustered damage is produced efficiently by the low-energy electrons that are set in motion, mostly as secondary particles, by α, β, γ, X and Auger electron emissions from radionuclides as well as from external radiations. The more complex forms of damage common to these sources are potentially unique to ionizing radiation, as compared with those that occur spontaneously or are caused by other DNA-damaging agents. For increasingly complex lesions, accurate repair is believed to become progressively more unlikely, leading to increased probabilities of gene mutation, chromosomal aberration or cell death. The types of initial DNA damage produced by all forms of ionizing radiation are essentially similar, but the quantity of damage and the range of complexity depend on the type of radiation and whether the radiation is produced at sites on or near the DNA.

In vitro, various effects have been observed in a wide variety of cells, including DNA double-strand breaks, chromosomal and chromatid aberrations, gene mutation and morphological transformation, after irradiation with α-particle-emitting radionuclides, β-particle emitters, Auger electron emitters or characteristic low-energy X-rays. Cells morphologically transformed by α-particles and X-rays *in vitro* have been observed to cause tumours after their injection into mice. Similar effects have been observed directly with the pure β-particle emitters hydrogen-3 and carbon-14, the mixed β-emitter iodine-131, the Auger electron emitters indium-111 and iodine-125, pure (filtered) α-emissions from polonium-210 and plutonium-238 and other radionuclides with mixed or pure emissions.

The full range of cellular effects can be induced by any type of ionizing radiation, as is to be expected from the commonality of DNA damage, if the radiation particles or photons enter the cell nucleus to deliver a local dose.

The presence of chromosomal aberrations in human peripheral blood lymphocytes is a recognized indicator of exposure to radiation *in vivo*, an increase in the frequency of chromosomal aberrations above the background level reflecting direct exposure of circulating lymphocytes and/or haematopoietic precursor cells in the bone marrow. Increased frequencies of aberrations were observed in a number of studies after exposure of humans or experimental animals to either α- or β-particle-emitting radionuclides. Internal exposure of rodents to α- and β-particle-emitting radionuclides was shown to produce chromosomal alterations. Chromosomal aberrations and gene mutations were also observed in many studies in cells of people exposed internally to specific radionuclides, including the β-particle emitters hydrogen-3, phosphorus-32, yttrium-90 and iodine-131 and mixed α-particle emissions from Thorotrast (thorium-232 and its decay products).

5.5 Evaluation

There is *sufficient evidence* in humans that therapeutic injection of radium-224 causes bone sarcomas.

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

There is *sufficient evidence* in humans that ingestion of radium-228 causes bone sarcomas.

There is *sufficient evidence* in humans that diagnostic injection of thorium-232 as stabilized thorium-232 dioxide in colloidal form (Thorotrast) causes primary liver cancer, including haemangiosarcomas, and leukaemia, excluding chronic lymphocytic leukaemia.

There is *inadequate evidence* in humans for the carcinogenicity of thorium-232 after inhalation.

There is *inadequate evidence* in humans for the carcinogenicity of radon-220 (thoron) from internally deposited thorium-232.

There is *sufficient evidence* in humans that inhalation of plutonium-239 aerosols causes lung cancer, liver cancer and bone sarcoma. Exposure to plutonium-239 also entails exposure to plutonium-240 and other isotopes.

There is *inadequate evidence* in humans for the carcinogenicity of natural uranium.

There is *inadequate evidence* in humans for the carcinogenicity of polonium-210.

There is *sufficient evidence* in humans that exposure during childhood to short-lived radioisotopes of iodine, including iodine-131, in fall-out from reactor accidents and nuclear weapons detonations causes thyroid cancer.

There is *sufficient evidence* in humans that therapeutic ingestion or injection of phosphorus-32 administered as inorganic phosphate causes acute leukaemia.

There is *inadequate evidence* in humans for the carcinogenicity of strontium-90.

There is *inadequate evidence* in humans for the carcinogenicity of caesium-137.

There is *sufficient evidence* in experimental animals for the carcinogenicity of the pure α-particle emitter polonium-210.

There is *sufficient evidence* in experimental animals for the carcinogenicity of mixed α-particle emitters (radium-224, radium-226, thorium-227, thorium-228, thorium-230, thorium-232, neptunium-237, plutonium-238, plutonium-239 (together with plutonium-240), americium-241, curium-244, californium-249 and californium-252).

There is *limited evidence* in experimental animals for the carcinogenicity of natural uranium.

There is *inadequate evidence* in experimental animals for the carcinogenicity of uranium-233.

There is *sufficient evidence* in experimental animals for the carcinogenicity of pure β-particle emitters (hydrogen-3, phosphorus-32, strontium-90, yttrium-90, yttrium-91 and promethium-147).

There is *sufficient evidence* in experimental animals for the carcinogenicity of mixed β-particle emitters (iodine-131, caesium-137, cerium-144 and radium-228).

Overall evaluation

Radium-224 (^{224}Ra) and its decay products are *carcinogenic to humans (Group 1).*

Radium-226 (^{226}Ra) and its decay products are *carcinogenic to humans (Group 1).*

Radium-228 (^{228}Ra) and its decay products are *carcinogenic to humans (Group 1).*

Thorium-232 (^{232}Th) and its decay products, administered intravenously as a colloidal dispersion of $^{232}ThO_2$, are *carcinogenic to humans (Group 1).*

Plutonium-239 (^{239}Pu) is *carcinogenic to humans (Group 1).*

In making this overall evaluation, the Working Group noted that human exposure to ^{239}Pu may also include exposure to ^{240}Pu.

Phosphorus-32 (^{32}P) is *carcinogenic to humans (Group 1).*

Radioiodines are *carcinogenic to humans (Group 1).*

In making this overall evaluation, the Working Group noted that human exposure to radionuclides of iodine from atomic reactor accidents and nuclear weapons detonations is to iodine-131 (^{131}I) and additional short-lived isotopes.

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.

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 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 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.

SUMMARY OF FINAL EVALUATIONS

Agent	Degree of evidence of carcinogenicity		Overall evaluation of carcinogenicity to humans
	Human	Animal	
Pure α-particle emitters[1]			
Radon-222 and its decay products	S	S	1[2]
Polonium-210	I	S	
Curium-244 and its decay products		S[3]	
Mixed α-particle emitters[1]			
Radium-224 and its decay products	S	S	1
Radium-226 and its decay products	S	S	1
Radium-228 and its decay products	S		1
Thorium-232 and its decay products, administered intravenously as a colloidal dispersion of thorium-232 dioxide	S	S[3]	1
Thorium-232 and its decay products, after inhalation	I		
Radon-220, exhaled, from internally deposited thorium-232	I		
Thorium-227 and its decay products		S	
Thorium-228 and its decay products		S	
Thorium-230 and its decay products		S	
Uranium and its decay products, inhalation of ore dust containing uranium-234, uranium-235 and uranium-238	I	L	
Uranium-233 and its decay products		I	
Plutonium-238 and its decay products (may contain plutonium-240), after inhalation		S	
Plutonium-239 and its decay products (may contain plutonium-240), after injection		S	
Plutonium-239 and its decay products (may contain plutonium-240 and other isotopes), as aerosols	S	S	1
Neptunium-237 and its decay products		S	
Americium-241 and its decay products		S	
Californium-249 and its decay products		S	
Californium-252 and its decay products		S	
α-Particle-emitting radionuclides, internally deposited			**1**
Pure β-particle emitters[1]			
Hydrogen-3		S	
Phosphorus-32, as phosphate	S	S	1
Strontium-90	I	S	
Yttrium-90		S	
Yttrium-91		S	
Promethium-147		S	
Mixed β-particle emitters[1]			
Radioiodines, short-lived isotopes, including iodine-131, from atomic reactor accidents and nuclear weapons detonations (exposure during childhood)	S		1
Iodine-131		S	
Caesium-137 and its decay products	I	S	
Cerium 144 and its decay products		S	
Radium-228 and its decay products		S[4]	
β-Particle-emitting radionuclides, internally deposited			**1**

[1] See Section 3 of General Remarks for definition of pure and mixed emitters
[2] Previously evaluated (IARC, 1988)
[3] In two-year bioassays in rodents, curium-244 and thorium-232 may be considered pure α-particle emitters.
[4] In two-year bioassays in rodents, radium-228 may be considered a mixed β-particle emitter; during long-term exposure of humans to radium-228, the effects of α-radiation predominate.