The effects of ionising radiation on the kidneys

The radiosensitivity of the kidneys is a major factor restricting the applications of chemoradiotherapy. However, improved knowledge of the mechanisms involved has allowed new treatments to be developed that attenuate the effects of the irradiation or delay its consequences.

Ionising radiation is widely used for the treatment of cancer. Its curative properties depend of course on the radiosensitivity of the cancer cells, but its scope is also unfortunately limited by that of the surrounding tissues. Thus the radiosensitivity of the kidneys is a major factor restricting chemoradiotherapy applications. The clinical **irradiation** of the abdominal area or the whole body, as performed in the case of bone marrow transplants, is often accompanied by **nephropathies**, the evolution of which, although slow, can have a very unfavourable outcome.

The kidney is a regulating organ that maintains the stability and balance of the body's internal medium, against the quantitative and qualitative fluctuations of dietary intake. This function is assumed jointly by **epithelial** cells forming the **nephrons** (Box 1) and **endothelial** cells forming blood vessels. There are no fewer than about thirty different cell types in the kidney, each possessing a **phenotype** specific to its particular functions. These remarkably diverse cells respond differently, according to their phenotype, to the many kinds of aggression to which they are physically subjected. It would be surprising not to find the same diversity in their response to irradiation.

As regards aggression due to ionising radiation, the picture is so far relatively global. Briefly, a distinction is made between the effects produced on the blood vessels, on the **glomeruli**, which produce the ultrafiltrate from the blood that enters the renal **tubules**, and on the interstitial cells that surround these different structures.

Radiation nephropathy

The "threshold" above which kidney damage can occur is set at 20-25 **grays** (Gy), according to the **dose**/frequency pattern of the application. Tolerance is improved if the doses are split and given at wide intervals. The doses used for whole-body irradiation are kept below this threshold (e.g., 12-14 Gy, in 2 Gy fractions) to minimise the risk of kidney damage, which even so remains possible.

During the months following irradiation, an acute renal insufficiency can appear, marked by diminished glomerular filtration, which can be accompanied by reduced urinary flow rate, according to the intensity of the irradiation. The occurrence of acute kidney failure at this stage does not mean that chronic kidney failure is bound to develop later on.

Chronic kidney failure is a slowly evolving condition. Radiation, by damaging **DNA**, impairs cell function, and cell death occurs either by **apoptosis**, if the damage is severe, or, more frequently, when the cell divides. It can therefore occur several years (5 to 10) after irradiation, because the rate of cell renewal in normal kidney tissue is very slow compared, for example, with bone marrow or gastro-intestinal tissues. The clinical signs are proteinuria (presence of **proteins** in urine), elevated blood nitrogen and benign or malignant hypertension.

Currently it is estimated that out of 20,000 patients who undergo total irradiation for a bone marrow transplant, 20% go on to develop chronic kidney failure.

The radiation treatment of cancer is often accompanied by chemotherapy, the nephrotoxic effects of which add to those of the irradiation.

Anatomo-physiological modifications

The histological examination of biopsies shows glomerular damage, with **fibrin thrombi**, subendothelial deposits and capillary breaks, along with piecemeal tubular **necrosis** over short distances along the nephron.

For obvious ethical reasons it is impossible to study the causes of radiation-induced renal damage in humans. However, the similarity of the physiopathological mechanisms observed experimentally in different animal species (mice, rats, pigs, monkeys, etc.) suggests the processes are general.

At the nephron

All the functional parts of the kidney are affected by irradiation, but glomerular damage, marked in particular by the destruction of mesangial(1) cells and by clot-forming fibrin deposits, very likely occurs first. These effects seem to be the result of the release by the endothelial (and possibly mesangial) cells of the glomeruli, of a certain number of mediators, in particular the transforming growth factor TGF β1, a fibrogenic **cytokine** strongly implicated in the appearance of fibrosis in the kidney and other organs, but the findings are still conflicting. It is likely that the glomerular damage results, at least in part, from the release by the kidney of endothelins(2), which cause prolonged vasoconstriction of the renal microcirculation. It is possible that vascular thrombosis results from the change in the cell activities that favour coagulation (secretion of Willebrand's factor, or **activation** of plasminogen activator inhibitor PAI-1, which inhibits **fibrinolysis**).

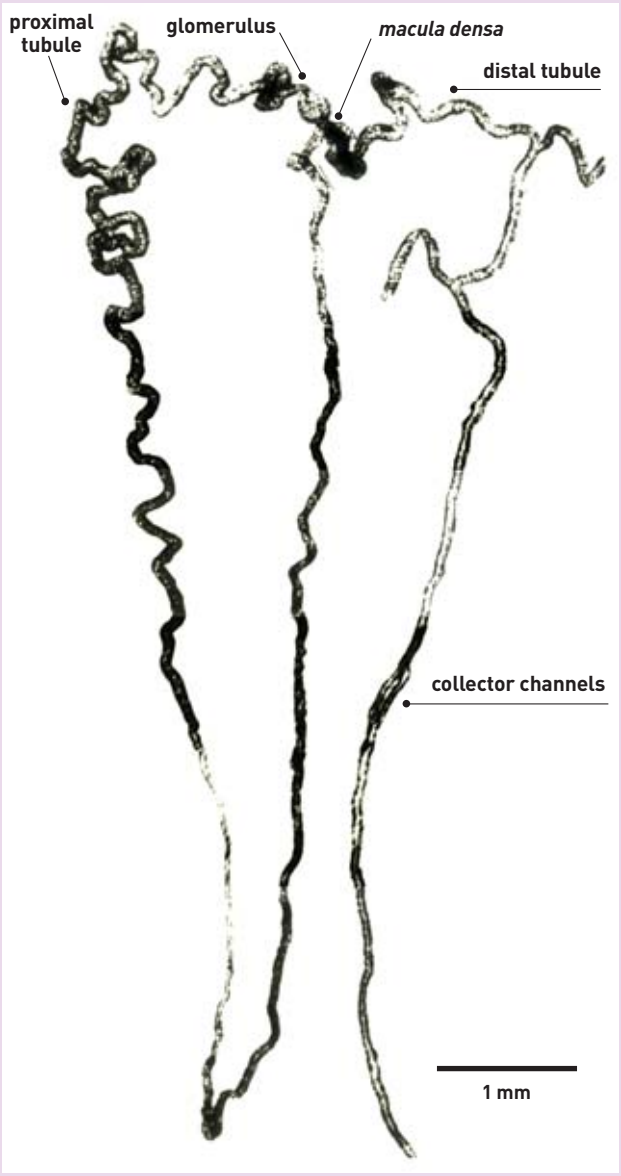
Along the nephron, the necrosis of certain cells (but not all), causes the surviving cells to attempt to make up the deficit, which can eventually lead to the destruction of a greater number of cells, which die only when they divide, because of DNA damage

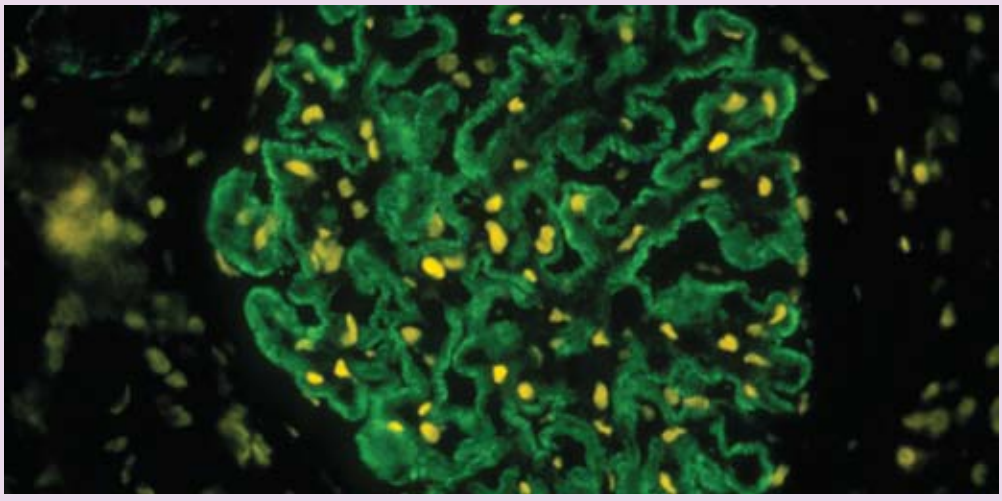
(1) **Mesangial** cells: interglomerular cells of the kidney supporting the capillaries that can behave as **macrophages** (see Box 1).

(2) Endothelin is a **hormone**; it is a small **protein** (a **peptide** with 21 amino acids) that causes an increase in arterial blood pressure by vasoconstriction (it is the most powerful vasoconstrictor known to date).

The nephron, a basic component of the kidney

The kidney is composed of tubular structures, the *nephrons* (1,000,000 in man) that all operate in parallel. The nephrons are irrigated by a vascular system that encloses them and supplies blood to the initial structures of the nephrons, the *glomeruli*. The blood is ultrafiltered by these glomeruli. This process only allows water, dissolved substances and **proteins** smaller than 60 kilodaltons (kD) to enter the lumen of the nephron. Each glomerulus is composed of a vascular part (a "clump" of capillaries) alongside a tubular part formed of **epithelial** cells. Mesangial cells occupy the space between these two parts. At a precise point on the distal segment of the nephron, the *macula densa*, the tubule comes into contact with the glomerulus. This anatomical loop supports a regulatory loop. According to the flow rate of sodium at this point, an array of **mediators** is elicited to decrease or increase the glomerular filtration rate, so as to attenuate, in the last segments of the nephron, the variations of flow rate that may arise upstream, in particular at the *proximal* level. These mediators include the renin-angiotensin system. Renin is released by the cells of the *macula densa*, and a "conversion" **enzyme** then forms, from this renin, angiotensin II, a powerful vasoconstrictor acting on the glomerular arterioles, which control the quantity of ultrafiltrate entering the nephron.





R. Oriol/Inserm/DR

The nephron, the functional unit of the kidney, is composed of a glomerulus and a tubule. Close up, cryostat microfluorescence section (section of deep frozen biopsy) of a glomerulus in a patient with extramembranal glomerulonephritis. Green: extramembranal antibody deposits (immunoglobulins) Yellow: nuclei of the mesangial cells.

	cadmium (Cd)	uranium (U)
daily amount in food	50 µg/day in non-smokers	2 µg/day on average (but wide variation from 0.5 µg to several hundred µg according to location)
other exposure routes	inhalation (occupational, tobacco use ++)	inhalation (occupational, environmental) the insoluble forms are retained in the lungs and related lymphatic system
gastro-intestinal absorption (f1) in adults	3-7%	2%
binding in plasma	metallothionein	bicarbonates, transferrin, surface of red cells
main deposit organs, "store"	liver, kidney	skeleton (+ lung for inhaled soluble forms)
biological half life	10-30 years cumulative kidney toxin	a few days for a large fraction of incorporated U
target cells	proximal tubular cells and glomerular damage	proximal tubular cells and glomerular damage at high dose
human renal concentration considered non-toxic	200 µg/g	3 µg/g
biological monitoring • urine assay of the element	• Cd	• U
• measurement of indirect indicators (non-specific)	• beta-2 microglobulin, retinol binding protein (RBP), metallothionein, etc.	• glucose and LDH, beta 2 microglobulin, etc.
monitoring criterion for occupational exposure ("continuous" chronic exposure)	urine Cd < 5 µg/g of creatinine (corresponds to cumulative toxicity) *source: INRS*	urine U < 35 µg/g of creatinine *source: CEA*

Tableau.
Comparison of the effects of cadmium and uranium on the kidneys.

in parent cells. Shortly after irradiation the cells show signs of apoptosis followed later (3 to 5 weeks in rats) by a proliferative response.
Renal **ischemia** resulting from irradiation in turn causes dysfunction of the proximal tubule, reducing re-absorption of water and sodium, which then depresses the function of the healthy glomeruli via the operation of a regulating loop (Box p. 49).

Direct and indirect treatments

Treatments now exist that can attenuate the effects of irradiation or delay their consequences. They work by protecting glomerular function, by acting either directly at the glomeruli (by inhibition of coagulation factors or anti-fibrinolytic factors), or indirectly by countering the action of the regulating loop. In the latter case, two types of treatment are currently used: they either inhibit the conversion **enzyme** (captopril) or block the angiotensin II **receptors** (Box).

Internal contamination

Uranium is an **internal contamination** agent that like cadmium, lead and mercury produces effects on the kidney similar to those of Fanconi's syndrome, namely impaired proximal tubular function resulting mainly in elevated urine amino-acids. In fact, all the proximal functions are progressively affected, so that the renal re-absorption of not only **amino acids** but also of **electrolytes**, urea, sugars and water is adversely affected. The table opposite compares, as an example, the effects of cadmium and uranium on the kidneys.

Cogema/Marcoule

Testing for the presence of actinides in the urine of personnel during routine radiotoxicological analysis carried out by the medical analysis laboratory at CEA Marcoule.

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A Natural and artificial radioactivity

Everything on the earth's surface has always been exposed to the action of ionising radiation from natural sources. Natural radiation, which accounts for 85.5% of total radioactivity (natural plus artificial), is made up of 71% telluric radiation and about 14.5% cosmic radiation. The radionuclides formed by the interaction of **cosmic rays** arriving from stars, and especially the Sun, with the nuclei of elements present in the atmosphere (oxygen and nitrogen) are, in decreasing order of dose (Box F, *From rays to dose*) received by the population, carbon-14, beryllium-7, sodium-22 and tritium (hydrogen-3). The last two are responsible for only very low doses.

Carbon-14, with a half life of **5,730 years**, is found in the human body. Its activity per unit mass of carbon has varied over time: it has diminished as carbon dioxide emissions from the combustion of fossil fuels have risen, then was increased by atmospheric nuclear weapon tests.

Beryllium-7, with a half life of **53.6 days**, falls onto the leaf surfaces of plants and enters the body by ingestion (Box B, *Human exposure routes*). About 50 Bq (becquerels) per person per year of beryllium-7 are ingested.

The main or **"primordial" radionuclides** are potassium-40, uranium-238 and thorium-232. Along with their radioactive decay products, these elements are present in rocks and soil and are therefore found in many building materials. Their concentrations are generally very low, but vary according to the nature of the mineral. The gamma radiation emitted by these radionuclides forms the **telluric radiation**, which is responsible for the external exposure of the body. The primordial radionuclides and many of their long-lived descendants are also found in trace amounts in drinking water and plants: this results in an internal exposure by ingestion, plus an additional low exposure by inhalation of airborne suspended dust particles.

Potassium-40 is a beta and gamma emitter with a half life of **1.2 thousand million years**, and has no radioactive descendants. This radioactive isotope makes up 0.0118% of all natural potassium, and enters the body by ingestion. The mass of natural potassium in the human body is independent of the quantity ingested.

Uranium-238 is an alpha emitter with a half life of **4.47 thousand million years**. It has thirteen main alpha-, beta- and gamma-emitting radioactive descendants, including **radon-222** (**3.82 days**) and **uranium-234** (**0.246 million years**). Uranium-238 and its two descendants **thorium-234** (**24.1 days**) and **protactinium-234m**(1) (**1.18 min**), and **uranium-234** are essentially incorporated by ingestion and are mainly concentrated in the bones and kidneys.

Thorium-230, derived from uranium-234, is an alpha emitter with a period of **80,000 years**. It is an osteotrope, but enters the body mainly by the pulmonary route (inhalation). **Radium-226**, a descendant of thorium-230, is an alpha emitter with a half life of **1,600 years**. It is also an osteotrope and enters the body mainly *via* food. Another osteotrope, **lead-210** (**22.3 years**), is incorporated by inhalation though mostly by ingestion.

Thorium-232 is an alpha emitter with a half life of **14.1 thousand million years**. It possesses ten main alpha-, beta- and gamma-emitting radioactive descendants including **radon-220** (**55 s**). Thorium-232 enters the body mainly by inhalation. **Radium-228**, a direct descendant of thorium-232, is a beta-emitter with a half life of **5.75 years**. It enters the body mainly in food.

Radon, a gaseous radioactive descendant of uranium-238 and thorium-232, emanates from the soil and building materials, and along with its short-lived alpha-emitting descendants constitutes a source of internal exposure through inhalation. Radon is the most abundant source of natural radiation (about 40% of total radioactivity).

The human body contains nearly 4,500 Bq of potassium-40, 3,700 Bq of carbon-14 and 13 Bq of radium-226 essentially imported in food.

Natural radiation is supplemented by an anthropic component, resulting from the medical applications of ionising radiation and to a lesser extent from the nuclear industry. It accounts for about 14.5% of the total radioactivity worldwide, but much more in the developed countries. In the medical field (more than 1 mSv/year on average in France), irradiation by external sources predominates: radiodiagnosis (X-rays) and radiotherapy, long based on cæsium-137 and cobalt-60 sources, but now more and more often using linear accelerators. Irradiation by internal routes (curietherapy with iridium-192) has more specialised indications (cervical cancer, for example). The metabolic and physicochemical properties of some twenty radionuclides are put to use for **medical activities** and in **biological research**. The medical applications comprise radiodiagnostics (scintigraphy and radio-

(1) m for metastable. A nuclide is said metastable when a transition delay exists between the excited state of the atom and the stable one.

immunology), and treatment, including thyroid disorders using iodine-131, radioimmunotherapy in certain blood diseases (phosphorus-32) and the treatment of bone metastasis with strontium-89 or radiolabelled phosphonates alongside other uses of radiopharmaceuticals. Among the most widely used radionuclides are: **technetium-99m** (half life **6.02 hours**) and **thallium-201** (half life **3.04 days**) (scintigraphy), **iodine-131** (half life **8.04 days**) (treatment of hyperthyroidism), **iodine-125** (half life **60.14 days**) (radioimmunology), **cobalt-60** (half life **5.27 years**) (radiotherapy), and **iridium-192** (half life **73.82 days**) (curietherapy). The average contribution of radiological examinations to total radioactivity amounts to 14.2%.

The **early atmospheric nuclear weapon tests** scattered fallout over the whole of the earth's surface and caused the exposure of populations and the contamination of the food chain by a certain number of radionuclides, most of which, given their short radioactive half lives, have now vanished. There remain **cæsium-137** (**30 years**), **strontium-90** (**29.12 years**), some **krypton-85** (**10.4 years**) and **tritium** (**12.35 years**), and the isotopes of **plutonium** (half lives **87.7 years** to **24,100 years**). Currently, the doses corresponding to the fallout from these tests are essentially attributable to fission products (cæsium-137) and to carbon-14, rather than activation products and plutonium.

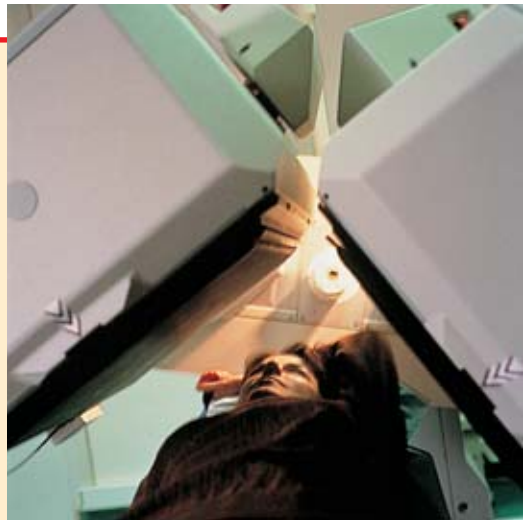
In the **Chernobyl accident** (Ukraine), which occurred in 1986, the total radioactivity dispersed into the atmosphere was of the order of 12 milliard milliard (10^{18}) becquerels over a period of 10 days. Three categories of radionuclides were disseminated. The first consisted of volatile fission products such as **iodine-131**, **iodine-133** (**20.8 hours**), **cæsium-134** (**2.06 years**), **cæsium-137**, **tellurium-132** (**3.26 days**). The second was composed of solid fission products and actinides released in much smaller amounts, in particular the strontium isotopes ^{89}**Sr** (half life **50.5 days**) and ^{90}**Sr**, the ruthenium isotopes ^{103}**Ru** (half life **39.3 days**) and ^{106}**Ru** (half life **368.2 days**), and **plutonium-239** (**24,100 years**). The third category was rare gases which although they represented most of the activity released, were rapidly diluted in the atmosphere. They were mainly **xenon-133** (**5.24 days**) and **krypton-85**.

The contributions of the early atmospheric nuclear weapon tests and the Chernobyl accident to the total radioactivity are roughly 0.2% (0.005 mSv) and 0.07% (0.002 mSv) respectively.

The whole of the **nuclear-powered electricity production** cycle represents only about 0.007% of total radioactivity. Almost all the radionuclides remain confined inside the nuclear reactors and the fuel cycle plants. In a nuclear reactor, the reactions that take place inside the fuel yield transuranics. **Uranium-238**, which is non-fissile, can capture neutrons to give in particular plutonium isotopes ^{239}**Pu**, ^{240}**Pu** (half life **6,560 years**) and ^{241}**Pu** (half life **14.4 years**), and **americium-241** (**432.7 years**). The main fission products generated by the fission of **uranium-235** (**704 million years**) and **plutonium-239** are **iodine-131**, **cæsium-134**, **cæsium-137**, **strontium-90** and **selenium-79** (**1.1 million years**).

The main radionuclides present in releases, which are performed in a very strict regulatory framework are, in liquid release, **tritium**, **cobalt-58** (**70.8 days**), **cobalt-60**, **iodine-131**, **cæsium-134**, **cæsium-137** and **silver-110m** (**249.9 days**). In gaseous releases **carbon-14** is the most abundant radionuclide, emitted most often as carbon dioxide. In all the reactors in the world, the total production of radiocarbon dioxide amounts to one tenth of the annual production formed naturally by cosmic radiation.

In addition, certain radionuclides related to the nuclear industry exhibit chemical toxicity (Box D, *Radiological and chemical toxicity*).



Laurence Médard/CEA

Classical scintigraphy performed at the Frédéric-Joliot Hospital Service (SHFJ). The gamma-ray camera is used for functional imaging of an organ after administration, usually by the intravenous route, of a radioactive drug (radiopharmaceutical) to the patient. The radionuclides used are specific to the organ being studied: for example, technetium-99m for the kidneys and bones, thallium-201 for the myocardium. The injected radiopharmaceutical emits gamma photons, which are captured by two planar detectors placed at 180° or 45° according to the examination.

B Human exposure routes

Human **exposure**, i.e., the effect on the body of a chemical, physical or radiological agent (irrespective of whether there is actual contact), can be external or internal. In the case of **ionising radiation**, exposure results in an energy input to all or part of the body. There can be direct **external irradiation** when the subject is in the path of radiation emitted by a radioactive source located outside the body. The person can be irradiated directly or after reflection off nearby surfaces.

The irradiation can be **acute** or **chronic**.

The term **contamination** is used to designate the deposition of matter (here **radioactive**) on structures, surfaces, objects or, as here, a living organism. Radiological contamination, attributable to the presence of **radionuclides**, can occur by the **external** route from the receptor medium (air, water) and vector media (soils, sediments, plant cover, materials) by contact with skin and hair (cutaneous contamination), or by the **internal** route when the radionuclides are **intaken**, by **inhalation** (gas, particles) from the atmosphere, by **ingestion**, mainly from foods and beverages (water, milk), or by penetration (injury, burns or diffusion through the skin). The term **intoxication** is used when the toxicity in question is essentially chemical.

In the case of **internal contamination**, the dose delivered to the body over time (called the **committed dose**) is calculated for 50 years in adults, and until age 70 years in children. The parameters taken into account for the calculation are: the nature and the intaken quantity of the radionuclide (RN), its chemical form, its **effective half life**[1] in the body (combination of **physical** and **biological half lives**), the type of **radiation**, the mode of exposure (inhalation, ingestion, injury, transcutaneous), the distribution in the body (deposition in target organs or even distribution), the radiosensitivity of the tissues and the age of the contaminated subject.

Lastly, the **radiotoxicity** is the toxicity due to the ionising radiation emitted by the inhaled or ingested radionuclide. The misleading variable called **potential radiotoxicity** is a *radiotoxic inventory* that is difficult to evaluate and made imprecise by many uncertainties.

(1) The effective half life (Te) is calculated from the physical half life (Tp) and the biological half life (Tb) by $1 / Te = 1 / Tp + 1 / Tb$.

F From rays to dose

Radioactivity is a process by which certain naturally-occurring or artificial **nuclides** (in particular those created by **fission**, the splitting of a heavy nucleus into two smaller ones) undergo spontaneous **decay**, with a release of energy, generally resulting in the formation of new nuclides. Termed **radionuclides** for this reason, they are unstable owing to the number of nucleons they contain (protons and neutrons) or their energy state. This decay process is accompanied by the emission of one or more types of **radiation**, ionising or non-ionising, and (or) particles. **Ionising radiation** is electromagnetic or corpuscular radiation that has sufficient energy to ionise certain atoms of the matter in its path by stripping electrons from them. This process can be *direct* (the case with alpha particles) or *indirect* (gamma rays and neutrons).

Alpha radiation, consisting of helium-4 nuclei (two protons and two neutrons), has low penetrating power and is stopped by a sheet of paper or the outermost layers of the skin. Its path in biological tissues is no longer than a few tens of micrometres. This radiation is therefore strongly ionising, i.e., it easily strips electrons from the atoms in the matter it travels through, because the particles shed all their energy over a short distance. For this reason, the hazard due to radionuclides that are **alpha emitters** is **internal exposure**.

Beta radiation, made up of electrons (beta minus radioactivity) or positrons (beta plus radioactivity), has moderate penetrating power. The particles emitted by **beta emitters** are stopped by a few metres of air, aluminium foil, or a few millimetres of biological tissue. They can therefore penetrate the outer layers of the skin.

Gamma radiation composed of high energy photons, which are weakly ionising but have high penetrating power (more than the **X-ray** photons used in radiodiagnosis), can travel through hundreds of meters of air. Thick shielding of concrete or lead is necessary to protect persons.

The interaction of **neutron radiation** is random, and so it is stopped only by a considerable thickness of concrete, water or paraffin wax. As it is electrically neutral, a neutron is stopped in air by the nuclei of light elements, the mass of which is close to that of the neutron.

• The quantity of energy delivered by radiation is the **dose**, which is evaluated in different ways, according to whether it takes into account the quantity of energy absorbed, its rate of delivery, or its biological effects.

• The **absorbed dose** is the quantity of energy absorbed at a point per unit mass of matter (inert or living), according to the definition of the International Commission on Radiation Units and Measurements (**ICRU**). It is expressed in **grays** (Gy): 1 gray is equal to an absorbed energy of 1 joule per kilogramme of matter. The *organ absorbed dose* is obtained by averaging the doses absorbed at different points according to the definition of the International Commission on Radiological Protection (**ICRP**).

• The **dose rate**, dose divided by time, measures the intensity of the irradiation (energy absorbed by the matter per unit mass and per unit time). The legal unit is the gray per second (Gy/s), but the gray per minute (Gy/min) is commonly used. Also, radiation has a higher **relative biological effectiveness (RBE)** if the effects produced by the same dose are greater or when the dose necessary to produce a given effect is lower.

• The **dose equivalent** is equal to the dose absorbed in a tissue or organ multiplied by a **weighting factor**, which differs according to the nature of the radiation energy, and which ranges from 1 to 20. Alpha radiation is considered to be 20 times more harmful than gamma radiation in terms of its biological efficiency in producing random (or **stochastic**) effects. The equivalent dose is expressed in sieverts (Sv).

• The **effective dose** is a quantity introduced to try to evaluate harm

Foulon/CEA

Technicians operating remote handling equipment on a line at the Atalante facility at CEA Marcoule. The shielding of the lines stops radiation. The operators wear personal dosimeters to monitor the efficacy of the protection.

in terms of whole-body stochastic effects. It is the sum of *equivalent doses* received by the different organs and tissues of an individual, weighted by a factor specific to each of them (weighting factors) according to its specific sensitivity. It makes it possible to sum doses from different sources, and both external and internal radiation. For internal exposure situations (**inhalation**, **ingestion**), the effective dose is calculated on the basis of the number of **becquerels** incorporated of a given radionuclide (**DPUI**, **dose per unit intake**). It is expressed in sieverts (Sv).

• The **committed dose**, as a result of internal exposure, is the cumulated dose received in fifty years (for workers and adults) or until age 70 (for those aged below 20) after the year of **incorporation** of the radionuclide, unless it has disappeared by physical shedding or biological elimination.

• The **collective dose** is the dose received by a population, defined as the product of the number of individuals (e.g., those working in a nuclear plant, where it is a useful parameter in the optimisation and application of the ALARA system) and the average equivalent or effective dose received by that population, or as the sum of the individual effective doses received. It is expressed in man-sieverts (man.Sv). It should be used only for groups that are relatively homogeneous as regards the nature of their exposure.

D Radiological and chemical toxicity

The chemical toxics linked to the nuclear industry include **uranium** (U), **cobalt** (Co), **boron** (B), used for its neutron-absorbing properties in the heat-exchange fluids of nuclear power plants, **beryllium** (Be), used to slow neutrons, and **cadmium** (Cd), used to capture them. Boron is essential for the growth of plants. Cadmium, like lead (Pb), produces toxic effects on the central nervous system. When the toxicity of an element can be both radiological and chemical, for example that of plutonium (Pu), uranium, neptunium, technetium or cobalt, it is necessary whenever possible to determine what toxic effects are radiological, what are chemical, and what can be either radiological or chemical (see *Limits of the comparison between radiological and chemical hazards*).

For **radioactive** elements with long physical **half lives**, the chemical toxicity is a much greater hazard than the radiological toxicity, as exemplified by rubidium (Rb) and natural uranium. Thus the chemical toxicity of uranium, which is more important than its radiological toxicity, has led the French regulators to set the **ingested** and **inhaled** mass limits for uranium in chemical compounds at 150 mg and 2.5 mg per day respectively, regardless of the **isotopic** composition of the element.

Certain metals or **metalloids** that are non-toxic at low concentrations can become toxic at high concentrations or in their radioactive form. This is the case for cobalt, which can be **genotoxic**, selenium (Se) (naturally incorporated in **proteins** or **RNA**), technetium (Tc) and iodine (I).

Cyrille Dupont/CEA

Two-dimensional gel electrophoresis image analysis carried out in the course of nuclear toxicology work at CEA Marcoule Centre in the Rhone Valley.