

## II. THE BIOLOGICAL BEHAVIOUR OF NUCLEAR TOXICS

After unravelling the mechanisms by which toxics are transferred from the environment to man (Chapter I), the second objective of research in nuclear toxicology is to make a detailed study of their behaviour in the body. The goal is to break down the mechanisms of their distribution, concentration and transformation in biological media at the cellular and intracellular levels, according to the forms present (gaseous, soluble or insoluble), and those of their transfer to target organs and cells. Determining the biochemical pathways that are disturbed by the elements in question will also help to explain how these exert their toxicity. Another important objective is to understand the effects of combined exposure, for which appropriate methods of comparison have to be developed.

Today, work is focused on model organisms the genomes of which have already been described, so that the tools of functional genomics and proteomics can be more easily used. The physiological effects of the toxics considered are studied using the most recent tools of molecular biology and genetics. The results are improving our understanding of how the toxics work at all the different levels of organisation of living forms – molecules, cells, tissues, organs and whole organisms.

This research covers *molecular radiotoxicology* (behaviour of radionuclides in biological media, mechanisms of membrane transport and of cell concentration) and *integrated radiotoxicology* (effects at the tissue and whole-organism level and biological mechanisms of transfer of radionuclides in living systems).

Research on molecular interactions between a nuclear toxic – whether or not it is a radionuclide – and its biological target (protein) is being considerably strengthened by the programme set in place by CEA.

Specific research concerns the main elements of interest – actinides (uranium, plutonium), fission and activation products (iodine, cobalt) or heavy metals (cadmium). Scientists are also engaged in describing processes specific to elements – not dealt with in this chapter – that are distributed more evenly in the body, such as caesium, and elements present in trace amounts in the body, such as zinc or selenium.

Depending on the way in which a radionuclide arrives in the body, its fate and the possible effects of the contamination can range widely. To evaluate fully and realistically the consequences of a possible internal contamination by a radionuclide it is therefore most important to study the way in which it is transported in the body, whether and how it binds to different tissues and organs, and by what means it is likely to be eliminated.

# The fate of radionuclides in the body

Certain nuclear toxics that exhibit a special affinity for the bone matrix are stored in the skeleton, where they can be retained for nearly a hundred years.

After **internal contamination**, the fate in the body of **elements** can be evaluated using the tools (models and associated parameters) proposed for risk assessment according to the legislation in force. In the case of **radionuclides**, the legislation is based on the recommendations of the **ICRP** which brought together all the existing data to design overall methods suitable for all **isotopes**. These models are applicable to workers and to the general population, allowing for different

age groups. However, the level of validation of these data is very wide ranging according to the nature of the element. Also the **speciation** of the elements (see *Speciation in the environment and in biological media*) can modify their transfer and their behaviour in the body. To obtain realistic evaluations, it is therefore advisable to use specific parameters when these are measured using recognised methods.

## The gateways into the body

The main gateways through which elements arrive in the body are **ingestion** and **inhalation**. Another gateway, the **transcutaneous route** by natural penetration through the epidermis or after injury, is sometimes preponderant (Box B, *Human exposure routes*). The fate of the elements depends on their speciation and their physiological role. Three physicochemical forms can be distinguished: gaseous, soluble and “insoluble”.

Gases are absorbed essentially by the respiratory route. Their fate depends on their chemical reactivity towards the constituents of the air-tissue interface and their solubility in different organic media.

“Insoluble” forms are cleared at the entry point by transport and after dissolution (see soluble forms below), in the knowledge that even the most “insoluble” forms have a solubilisable fraction. After ingestion, they are eliminated naturally by gastro-intestinal transit. After inhalation, the **mucociliary** clearance of the tracheobronchial tree helps mechanically to send some of the particles deposited to the digestive tract, the rest being cleared by the **lymphatic route** towards regional lymph nodes. Only this lymphatic clearance is involved after deep injury.

Models have been developed to describe the fate of elements after ingestion or inhalation. The digestive tract model is particularly simple (Figure 1, p. 23). It takes into account the residence time of food inside different **compartments** and a fraction transferred to the bloodstream from the stomach or the anterior part of the small intestine. The ICRP is currently working on a more representative model. In contrast, the respiratory tract model is much more complex. In particular it takes into account the **particle size distribution** of **aerosols**, which determines their distribution pattern in the different thoracic and extra-thoracic compartments, the clearance of inhaled particles by transport and dissolution, and individual physiology (Box).



Harnett/Harzon/PhotoDisc

## The respiratory tract model

The particle size of **aerosols** modulates their deposition in the different **compartments** of the respiratory tract (Figure a). This particle size is described by the activity median aerodynamic diameter (AMAD) and the geometric standard deviation of the distribution ( $\sigma_g$ ). **ICRP 66** considers different compartments and describes a model that makes it possible to evaluate deposition of aerosols according to their physical

properties and the physiological characteristics of the individual (age, respiration pattern, type of activity). By default, from different measurements, it proposes a lower AMAD for the general population than for workers. The result is a much greater deposition deep in the lung, the filtering capacities of the upper airways being very efficient only for the largest particles (Figure a).

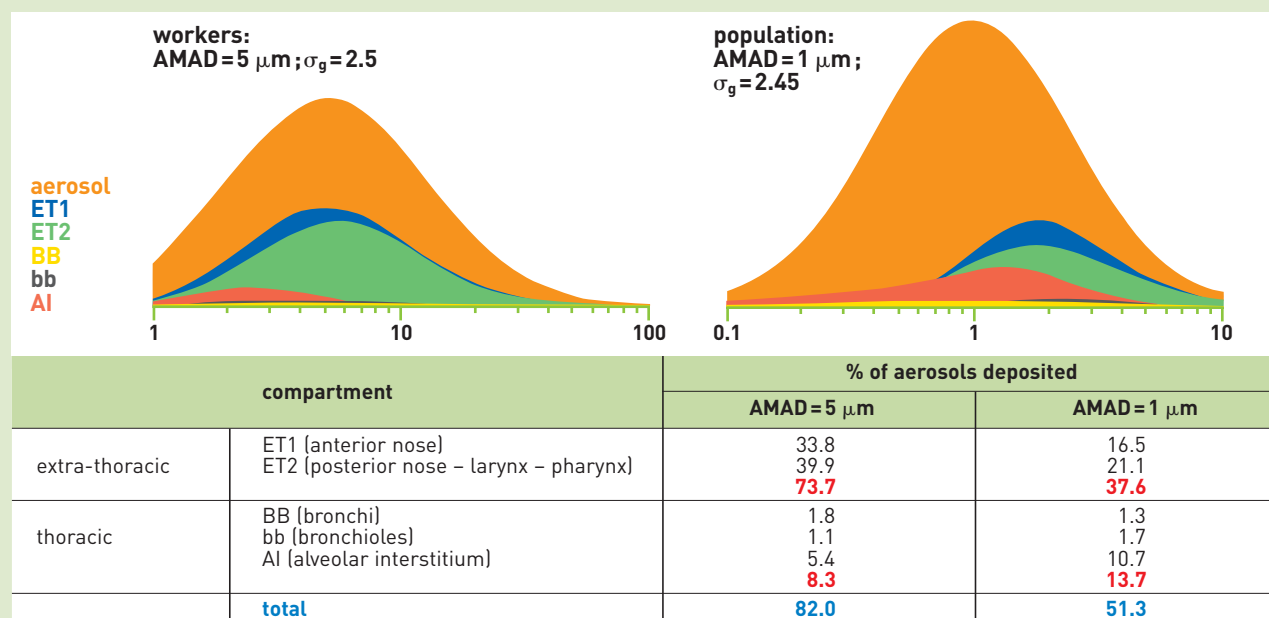


Figure a.  
Influence of particle size distribution on aerosol deposition.

The clearance of the respiratory tract implies both transport and dissolution of particles deposited after **inhalation** (Figure b). ICRP 66 considers different sub-compartments according to the deposition site: ET<sub>1</sub>, ET<sub>2</sub>, BB<sub>1</sub> and bb<sub>1</sub> at the air-tissue interface, BB<sub>2</sub> and bb<sub>2</sub> under the mucous film and ET<sub>seq</sub>, BB<sub>seq</sub> and bb<sub>seq</sub> for the particles that have penetrated the **epithelium**. The latter are transported by the **lymphatic route** to the regional lymph nodes, the others are transported to the digestive tract

by upward **mucociliary** clearance. The alveolar interstitium is divided into three compartments; only AI<sub>3</sub> can be cleared by the lymphatic route. The fraction transferred per day is stated. Simultaneously, particles dissolve, and various models are proposed to describe this process. The simplest model is depicted here, and the value of the parameters proposed by default is given for the compounds of type F (very soluble), M (moderately soluble) and S (sparingly soluble).

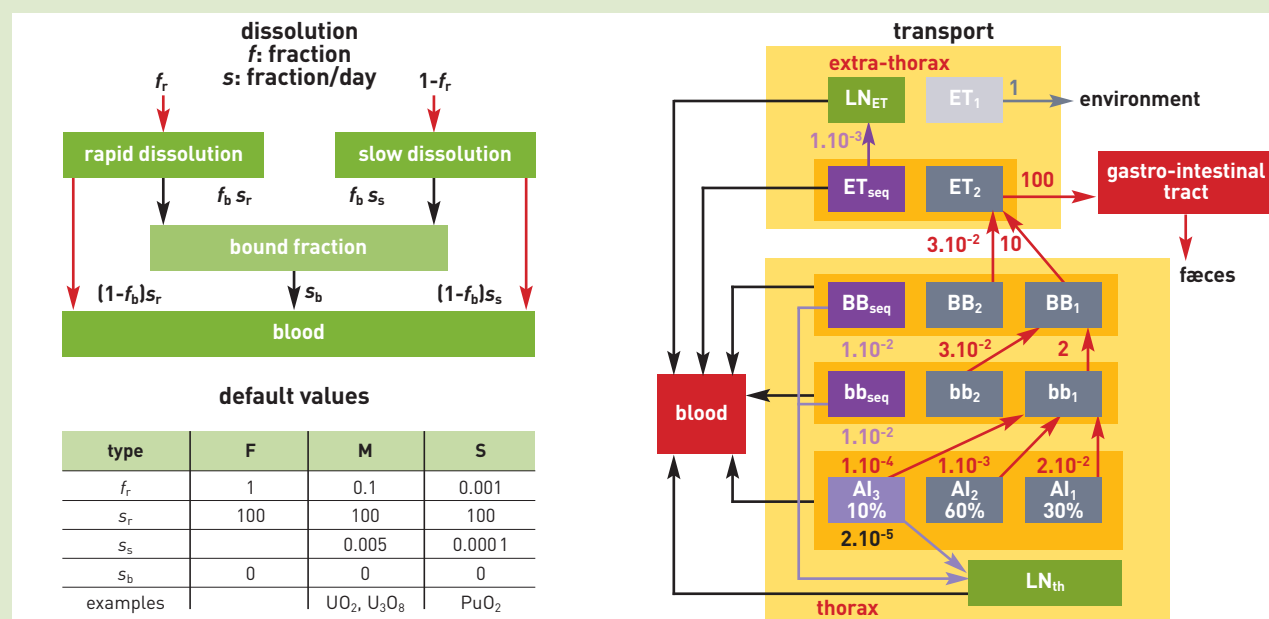


Figure b.  
Lung clearance by particle dissolution and transport. For the fractions, indices r, s, b stand respectively for rapid, slow, and bound. LN stands for lymph node.

## C Vital elements in the human body

Our daily diet supplies vital mineral salts and trace elements. Fresh vegetables are an important source of these nutrients.



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In addition to its main constituents carbon, hydrogen, oxygen and nitrogen (C, H, O, N), which are the building blocks of organic molecules, the substance of living organisms also contains vital **minerals** and **trace elements** necessary in particular for their growth and development. If the body's requirements for these elements are not met, it will develop deficiency disorders. In contrast, when supplied in excessive amounts these same elements can have toxic effects. Sometimes the safety margin between optimal provision and toxic threshold is very narrow.

**Mineral salts**, present in large quantities in the human body (about 4% by weight), are found in ionic form: calcium ( $\text{Ca}^{2+}$ ), potassium ( $\text{K}^+$ ), sodium ( $\text{Na}^+$ ), magnesium ( $\text{Mg}^{2+}$ ) as **cations**, chloride ( $\text{Cl}^-$ ), phosphorus and sulphur radicals as **anions**. These are eliminated continuously by the kidneys and so have to be supplied daily in sufficient amounts in food. These **electrolytes** together with water are vitally important

for certain biochemical and biophysical processes: tissue building, maintenance of cell hydration, participation in many **enzymatic** processes, involvement in the **metabolism** of glucids (sugars) and protids (**peptides**, **proteins**), etc. Certain cation movements are closely linked to activities of the brain, nerves, muscles, heart and glands.

**Calcium** is one of the major constituents of bone. It also plays an important role in blood clotting, muscle contraction and heart muscle function. In association with calcium, **phosphorus** is essential for the building of bone tissue. It is also involved in the absorption and processing of certain nutrients (food substances that can be assimilated). **Sodium** is the most important mineral in the human body fluids (the blood and all the other extracellular fluids). It helps to maintain the "internal medium" in a steady state, and its elimination or retention, through the kidneys, is one of the mechanisms that regulates arterial blood pressure. A diet too rich in sodium may often cause

an increase in blood pressure. The main intracellular mineral element is not sodium, but **potassium**. It helps to maintain cardiac automaticity and muscle activity in general. A shortage of potassium, in addition to harmful effects on the heart, sometimes causes cramp. **Magnesium** is involved in many biological processes in cells. Magnesium deficiency can cause muscle weakness, cramp, tetanic seizures and digestive disorders. **Trace elements** are the vital minerals required by living organisms in tiny amounts. Their absence is a cause of nutritional deficiency disorders and in some cases can arrest a particular function. They are present as compulsory micro-constituents of certain organic molecules that are necessary for basic reactions in cell metabolism. The vital trace elements include metals (iron, zinc, copper, manganese, molybdenum), **metalloids** (selenium), and **halogens** (iodine, fluorine). The trace metals are important because they occur in entities with high biochemical activities such as



## C (next)

**enzymes.** In enzyme metalloproteins, the metal atom is an integral part of the protein molecule and is located at the centre of the active site<sup>(1)</sup> of the enzyme. In an ionised state, the metal behaves as an activator of an enzyme protein, without actually forming part of it.

**Iron**, for example, makes up the active part of haemoglobin, the protein of red blood cells, and the cytochromes, proteins that transfer electrons during cell respiration. In enzyme metalloproteins it is present in the ferredoxins, biochemical substances involved in electron transport, and in various enzymes. A shortage of iron leads to anaemia, while an excess can be damaging to the heart. **Zinc** deficiency is sometimes the cause of dwarfism and underdevelopment of the male sex organs. Insufficient **copper**, which is vital for the generation of blood cells in the bone marrow (haematopoiesis), is also a cause of anaemia. **Selenium** seems to afford protection against certain cancers, and a lack of this element can cause diseases of the heart muscle. **Iodine** is essential for thyroid function. It is present in a hormone, thyroglobulin, which controls its metabolism. Lack of iodine causes enlargement of the thyroid gland (goitre) and delays physical and mental development in children. **Fluorine** deficiency is associated with defective mineralisation of bones and teeth (favouring caries).

**Contamination** by **radionuclides** can result in the replacement of these minerals and trace elements by radioisotopes (Box E, *When radionuclides take the place of vital elements*).

(1) Active site: region of an enzyme that effects the **catalysis** of a particular reaction.

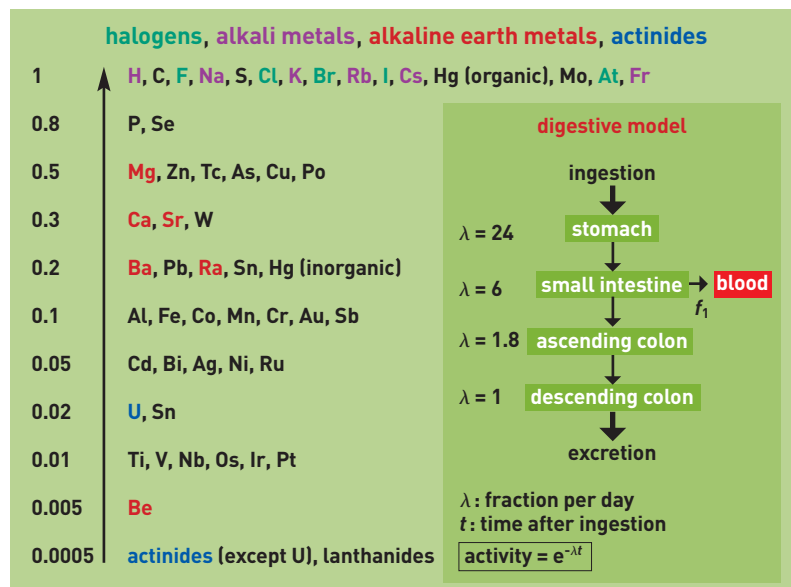


Figure 1. The digestive tract model. The value of  $f_1$ , fraction of the ingested quantity transferred to the blood, is stated here for different elements in adults (halogens, alkali metals, alkaline earth metals, actinides). The application of the precautionary principle favours the use of values sometimes equal to 1 for many elements. In the case of elements that are poorly assimilated, the value of  $f_1$  is multiplied by 10 to take into account the greater digestive absorption observed in children.

### Transfer to the bloodstream and biological fate

The *soluble forms* circulate in the body *via* various routes. The transfer of elements necessary for life (Box C, *Vital elements in the human body*) to the bloodstream is often facilitated by specific processes (respiration, digestion, ion transport, etc.). The other elements take similar routes, but their transport is often much less efficient than that of their biological analogues (Box E, *When radionuclides take the place of vital elements*).

Once this transfer has taken place, the elements remain in the blood for a certain residence time that reflects the balance between their rates of organ deposition and excretion. The kidneys, after **glomerular** filtration of chemical species with low molecular weight, eliminate, *via* the urine, the elements that are not reabsorbed along the **tubules**. Faecal excretion includes both the secretion of **electrolytes** by the gastro-intestinal mucosa and hepatic excretion by the biliary route. For some elements, sweat and exhalation are also non-negligible excretion routes.

The distribution of most of the essential elements and some of their analogues (e.g., sodium, chlorine, potassium, caesium) seems fairly homogeneous in **soft tissues**. However, some of them are able to accumulate in extracellular storage compartments such as the colloid of the **thyroid follicles** for iodine, and the bone matrix for **osteotropic** elements (calcium, barium, strontium, radium, and **transuranics**). The skeleton constitutes a storage site with a retention period that can be as long as several decades. This period is generally much shorter for soft tissue, though it can sometimes still be as long, e.g., for plutonium in the liver.

In fact, there are continuous exchanges between deposition sites and biological fluids. The modelling of **biokinetic** data has provided values for rates of

exchange between different compartments. In practical terms, the complexity of current models increases as the distribution of the elements in the body is more heterogeneous, and as their residence time is longer.

## Models of varying complexity

The simplest models are known as *non-recycling* models (Figure 2). They take into account the apparent residence time of elements in organs where they are deposited, and the fraction eliminated from the organ and excreted in the urine or faeces after a short time in the blood. This type of model is currently applied to many essential elements (sodium, potassium, chlorine, phosphorus, magnesium, zinc, cobalt, selenium, etc.) and also to most of their analogues and **transition metals**. For tritium, carbon and sulphur, the models make a distinction between different organic or inorganic chemical forms.

The most complex models are called *recycling* models (Figure 2). They take into account the continuous exchanges between blood and tissues. The iodine model is the simplest example. Much more complex models have been developed for the **alkaline earth metals**. They include numerous compartments and distinguish between different territories in the same tissue. These models are closer to the physiological reality. Models with analogous structures have been developed for lead and **actinides**. They prove especially well-suited to *a priori* estimation of the concentration of elements in different compartments of the body as a function of time after contamination (*top-down models*), and also, *a posteriori*, to evaluate levels of **exposure** from the measurement of retention and urinary and faecal excretion (*bottom-up models*).

The solution of a non-recycling model is accessible by a simple exponential calculation. However, specific software must be used for the recycling model, which is currently used to calculate **dose**.

## Towards more and more representative models

For special applications, for example to improve the efficacy of **decorporating** treatments, new much more complex recycling models can still be devised, taking into account in particular the speciation of the elements inside compartments more closely representative of cell and tissue physiology.

Work currently in progress focuses (i) on the uncertainties concerning the models and their associated parameters in order to direct experimental research to allow ranking of radionuclide toxicity and complete existing data, and (ii) on the influence of the speciation of the elements on their **biodistribution** after different types of contamination, giving special attention to the new compounds used in the nuclear industry.

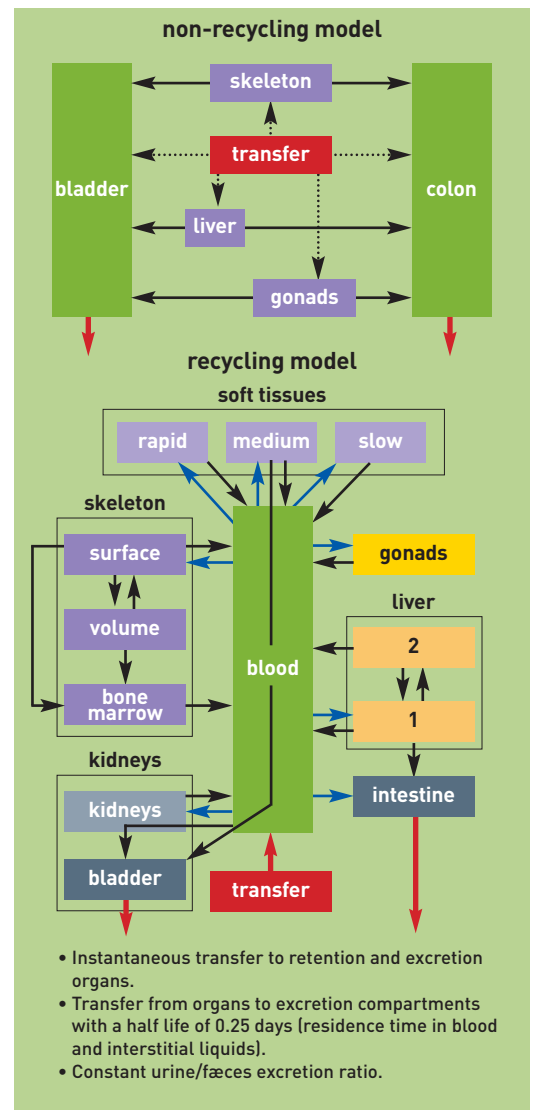


Figure 2. Non-recycling model (ICRP 30) and recycling model (ICRP 67) developed for plutonium. For the recycling model, many compartments are considered, but their physiological roles are often poorly understood. This is the case for example for the liver, where compartments 1 and 2 do not correspond to defined cells or structures, and for soft tissues assigned an "average" retention time, a fraction being eliminated directly in urine. The structure of the model makes it possible to know at any time the quantities of elements excreted or retained in the different compartments.

The results obtained will help to bring the models closer to reality and so allow better assessment of chemical and radiological risks and of exposure levels in any incident.

➤ **Paul Fritsch** and **Béatrice Le Gall**  
Life Sciences Division  
CEA-DAM-Ile de France Centre

# 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**<sup>(1)</sup> (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 caesium-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 physico-chemical properties of some twenty radionuclides are put to use for **medical activities** and in **biological research**. The medical applications comprise radio-diagnostics (**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 radionu-

clides 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  $^{89}\text{Sr}$  (half life 50.5 days) and  $^{90}\text{Sr}$ , the ruthenium isotopes  $^{103}\text{Ru}$  (half life 39.3 days) and  $^{106}\text{Ru}$  (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  $^{239}\text{Pu}$ ,  $^{240}\text{Pu}$  (half life 6,560 years) and  $^{241}\text{Pu}$  (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



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.

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**).



## B Human exposure routes

**H**uman **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**<sup>(1)</sup> 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 ( $T_e$ ) is calculated from the physical half life ( $T_p$ ) and the biological half life ( $T_b$ ) by  $1 / T_e = 1 / T_p + 1 / T_b$ .

# F From rays to dose

**R**adioactivity 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

## F (next)



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).



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



# E When radionuclides take the place of vital elements

**A**mong the **elements necessary for life** the human body contains a certain number of naturally-occurring **radioactive isotopes**. The main ones are carbon-14 and potassium-40, which are responsible for an intrinsic radioactivity of natural origin amounting to *several thousand becquerels* in an adult. In unusual or accidental situations, the body can also be **exposed** to toxic elements or isotopes. Among those used or generated by the nuclear industry, some are isotopes of physiologically vital elements, such as iodine, while others are non-physiological elements such as cadmium, strontium, caesium, lead and the **actinides**.

In addition, certain essential constituents of living matter, formed of stable elements such as iron, manganese or sulphur, have radioactive equivalents among certain **activation** or corrosion **products**.

Potential major radiocontaminants include three main groups of **radio-nuclides**: iodine ( $^{131}\text{I}$  and  $^{133}\text{I}$ ), strontium ( $^{89}\text{Sr}$  and  $^{90}\text{Sr}$ ) and caesium ( $^{134}\text{Cs}$  and  $^{137}\text{Cs}$ ). Iodine, which has a biological role, is very readily absorbed and **metabolised**, whereas strontium and caesium follow the same metabolic

pathways as vital **biogenic** elements. Thus strontium ( $^{90}\text{Sr}$ ) behaves much like calcium, and so ends up in bone tissue, of which calcium is a major constituent, while caesium ( $^{137}\text{Cs}$ ) diffuses throughout muscle tissue, following practically the same metabolic pathways as potassium, the main intracellular element.

Although these nuclides follow pathways similar to those by which the transfer to blood of vital elements takes place, often facilitated by specific processes (respiration, digestion, ion transport), the efficiency of their transport is often much lower than that of their biological analogues.

In the event of **contamination** by radionuclides, these can therefore take the place of vital minerals and trace elements. After **ingestion**, the metabolised fraction of the radionuclide is distributed throughout the body or is concentrated in particular organs. Although most of the essential elements and some of their analogues (sodium, chlorine, potassium, caesium, etc.) are distributed fairly evenly in **soft tissues**, some can accumulate in extracellular storage **compartments** such as the thyroid for iodine, the liver for plutonium

and the bone matrix for the so-called **osteotropic** elements (calcium, barium, strontium, radium and **transuranics**). Thus the membrane transporters facilitate the entry of caesium and rubidium into cells. Likewise, strontium can be efficiently accumulated in subcellular confinement compartments. Also, certain cotransporters responsible for the capture of **divalent** metals (iron, copper and zinc ions) also transfer cadmium. Lastly, the possibility that toxics (whether physiological or not) may be **sequestered** in each compartment by any of an array of soluble **proteins** must not be underestimated. Such trapping can be **covalent** (e.g., iodinated thyroglobulin).

Calcium, or proteins that **reduce** the free toxic forms of certain vital **transition metals** (iron, copper, selenium, etc.) are potential **complexing agents** for non-physiological elements such as uranium or cadmium. The latter metal has few specific effects but tends to take the place of calcium, zinc and copper. Its opportunistic behaviour, which can cause severe physiological disorders, is shared by many other **exogenous** metals.