The mechanisms responsible at the cell level for inducing toxic reactions after contamination are as yet only imperfectly known. Work still needs to be done for both contaminants that have a biological role, such as iodine, and those that do not, such as cadmium, uranium and plutonium. In particular, these mechanisms bring into play, in biological membranes, carriers which are the physiological partners responsible for material exchange with the environment or inside the body. As they lack absolute selectivity, these carriers, which are involved in the assimilation and accumulation of vital mineral elements, also have the ability to transport toxic elements and isotopes.

The mechanisms involved **at the cell level**

Can vital biological exchanges also be life-threatening?

Several elements and **isotopes** used or generated by the nuclear industry are considered as toxic for mammals. These are isotopes of physiologically vital elements (Box C, ***Vital elements in the human body***), such as iodine, or non-physiological elements such as cadmium, strontium, cæsium, lead and the **actinides**. During **contamination**, if the concentrations of toxic elements in the local environment are low, harmful effects are observed only after the elements have been assimilated, and sometimes concentrated or **sequestered** in the body. The molecular partners and the physiological mechanisms responsible for these effects are still only imperfectly known. Their identification is an important objective in research conducted by CEA (see box *The CEA Programme*).

Barriers and biological membranes

Different **biological barriers** (box) restrict the access of **exogenous** toxic elements to the blood **compartment**, to the **cytoplasm** of a cell or to functional subcellular compartments (**organelles** or **vesicular** microstructures). The biological membranes that govern flow through these barriers are formed by double-layered **lipid** envelopes, the hydrophobic central part of which prevents the free diffusion of hydrophilic molecules. Certain **proteins** inserted in the double layer favour specific exchanges with the immediate environment. The barrier located between the body and the local environment is materialised by a continuum of layers of **polarised** cells, or **epithelia**. The flows of hydrophilic substances through these layers are transcellular and involve successive movement through two differentiated domains of the membrane of the epithelial cells. In contrast, access to the cytoplasm of all the other cells of the body or to the other functional subcompartments is limited only by a single membrane (Figure 1).

Carriers and permeability mechanisms

The membrane transport proteins or **carriers** (box) **catalyse** in particular the physiological transfer of soluble mineral elements (**electrolytes**, metal ions) across biological membranes. More than a hundred such carriers are known to exist in mammals. In physiological conditions each carrier handles **the specific transfer of a particular element** (box). However, different carriers can contribute to the movement of the same element. They can be ubiquitous in biological membranes or highly localised when the cell functions are specialised. The *channel*-type carriers or "**facilitated diffusion proteins**" type (box) catalyse the spontaneous movement of ionic species (potassium ion K^+, sodium ion Na^+, calcium ion Ca^+, chloride ion Cl^-…). Others, called active transporters, derive the energy necessary for the accumulation of substrates from the **hydrolysis** of adenosine triphosphate (the *ATPases*, the *ABC* transporters [Figure 1]) or transmembrane ionic concentration gradients (*cotransporters*). The active transporters are mainly involved in the regulation of essential electrolyte levels (Na^+, K^+, Cl^-, magnesium ion Mg^{2+}, Ca^{2+}, phosphate ion PO_4^{2-}, etc.) in each compartment or in the capture and confinement of vital elements present in trace amounts in the environment (iodine, metal ions).
It has often been observed ***in vitro*** that because they are not absolutely specific, carriers also transfer toxic elements that have physicochemical properties close to those of natural substrates. Thus ATPase Na^+/K^+ and some K^+ channel transporters facilitate the entry of rubidium and cæsium into cells. Likewise, strontium can be efficiently accumulated by ATPase-Ca^{2+} in subcellular confinement compartments. In addition, certain cotransporters responsible for the capture of **divalent** metals (iron ion Fe^{2+}, copper ion Cu^{2+} or zinc ion Zn^{2+}, etc.) also transfer cadmium. Strategies of

Some definitions

The membranes of epithelial cells are characterised by two differentiated membrane domains: the *apical membrane*, in contact with the external environment, and the *basolateral membrane* at the interface with the internal medium. The boundary between these domains is formed by a crown of membrane **proteins** involved in intercellular contacts. The two membrane domains make use of different carriers.

The membrane carriers are made up of chains of **amino acids** linked by **peptide bonds**. Each polypeptide chain crosses the double lipid layer several times and alternately exposes strongly **polar** domains to the two aqueous media on either side of the double layer. The transmembrane domains, of spiral structure, are associated through essentially apolar interactions to delimit a central polar region. This region includes the substrate recognition site and sites of access from the membrane surface.

The molecular basis for their ionic selectivity is only known with certainty for a very small number of carriers (for example, ATPase-Ca^{2+}). The biological selectivity mechanisms imply the co-ordination of the dehydrated substrate by a small number of atoms belonging to the side chains of a few amino acids of the membrane domains (Figure). However, the co-ordination sites can accept elements with similar physicochemical properties owing to the flexibility of the carrier structures.

Lastly, a **"facilitated diffusion protein"** is a membrane protein that creates a generally specific route that favours the diffusion of a hydrophilic molecule across the hydrophobic membrane double layer.

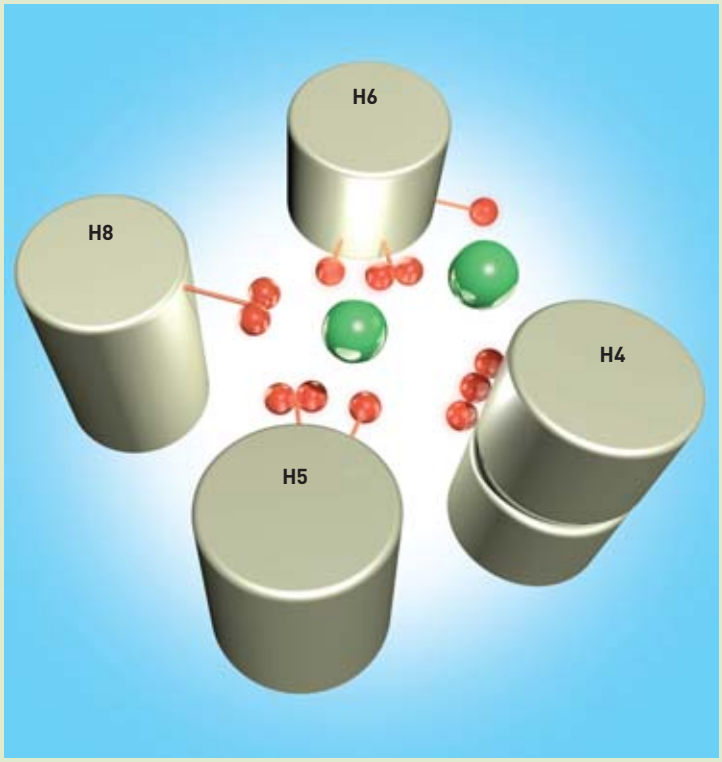


Figure.
Cross section of the membrane region of ATPase-Ca^{2+} showing the specific binding sites of the two calcium ions (green spheres). The oxygen atoms (red spheres) belonging to amino acids located on four different transmembrane spirals (brown cylinders, H4, H5, etc.) form a selective **co-ordination** "cage" for each **cation**.

gene invalidation(1) or genetic complementation(2) (**transgenesis**) and cellular or functional imaging methods ***in vivo*** are currently combined to identify the carriers and unravel the mechanisms responsible for inducing toxic reactions *in vivo* after contamination. Lastly, a possibility that should not be underestimated is the sequestration of physiological or non-physiological toxics in each compartment by a whole array of soluble proteins. The trapping can be **covalent** (for example, iodinated thyroglobulin). Calcium and proteins that **reduce** free toxic forms of certain vital **transition metals** (iron, copper, selenium, etc.) are potential **complexing agents** for non-physiological elements (uranium or cadmium).

(1) The invalidation strategy consists in introducing, in a targeted manner, a modification of the **sequence** coding for a healthy **gene**. This modification will cause the synthesis of a non-functional protein. For example, the excision of part of the gene sequence will result in the production of a truncated protein. Also, the introduction of a gene-reading shift may cause a complete change in the **amino acid** composition of the protein from the gene-reading shift site, for example.

(2) The gene complementation strategy is a method for compensating for the production of a deficient **mutant** protein by the production of a functional protein by introducing, randomly or in a targeted manner, a copy of the normal gene in at least one **chromosome**.

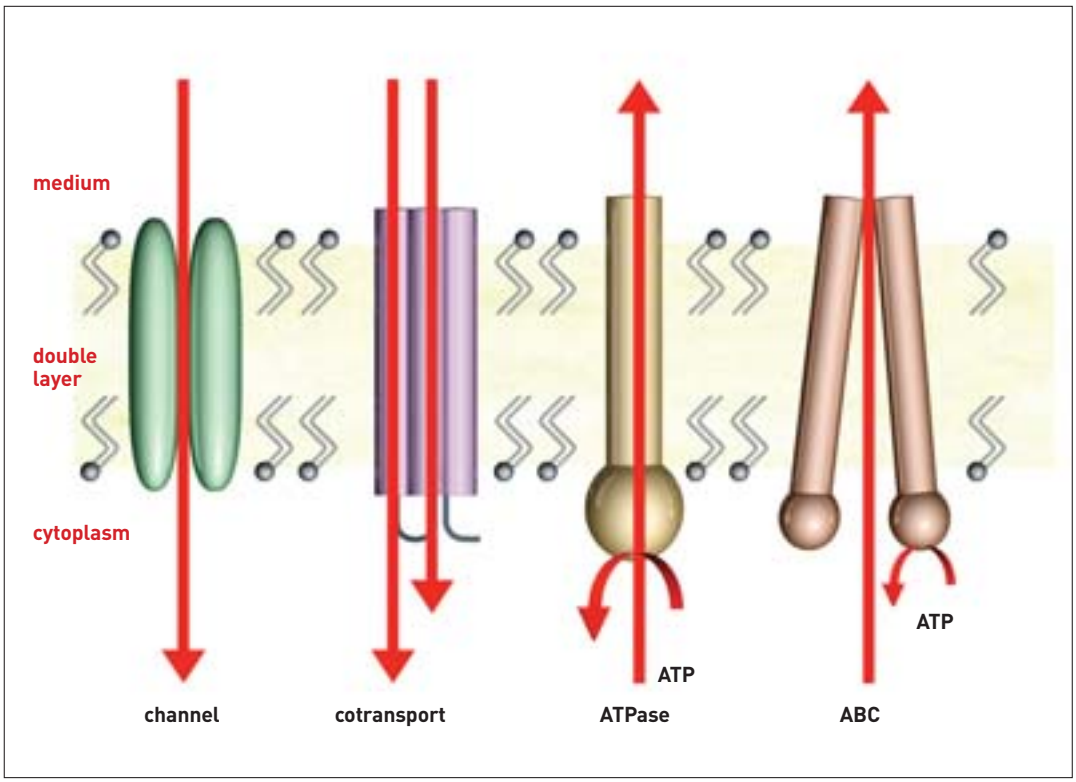
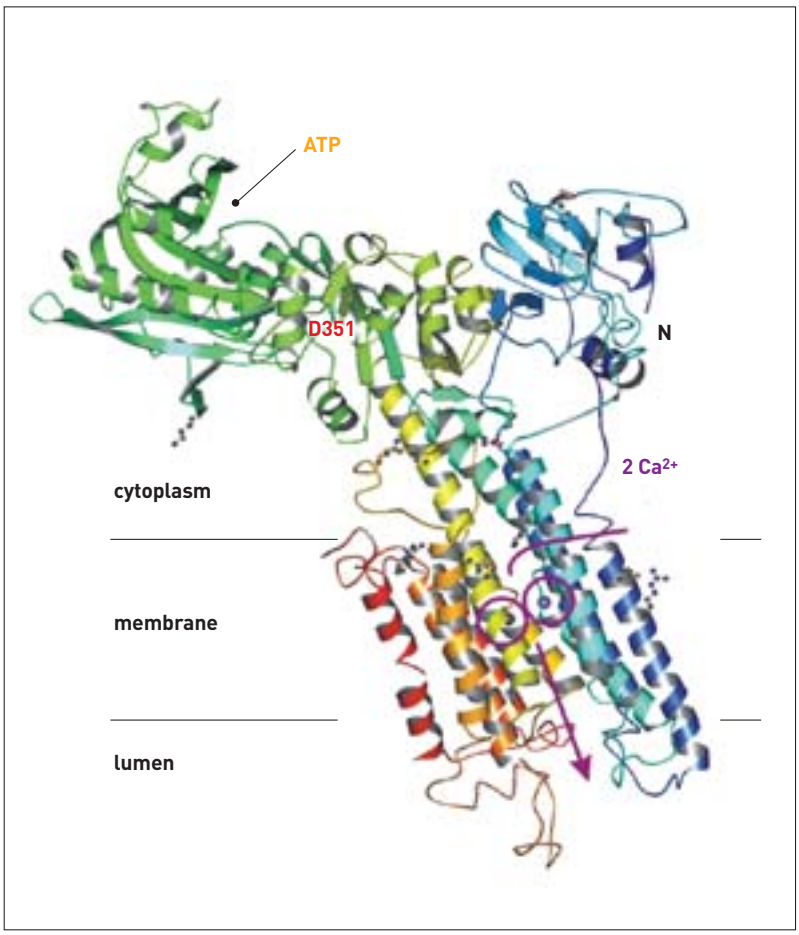


Figure 1.
Schematic representation of a biological membrane. The lipids form a molecular double layer, the hydrophobic interior of which forms a barrier to the free diffusion of hydrophilic substances and elements. Different types of carriers that cross the double layer are depicted.



C. Toyoshima, University of Tokyo, Japan

Structure of membrane ATPase-Ca^{2+}. The extra-membranal binding sites of ATP or the membranal binding sites of the two Ca^{2+} ions are shown by arrows.

Iodine, its isotopes and technetium

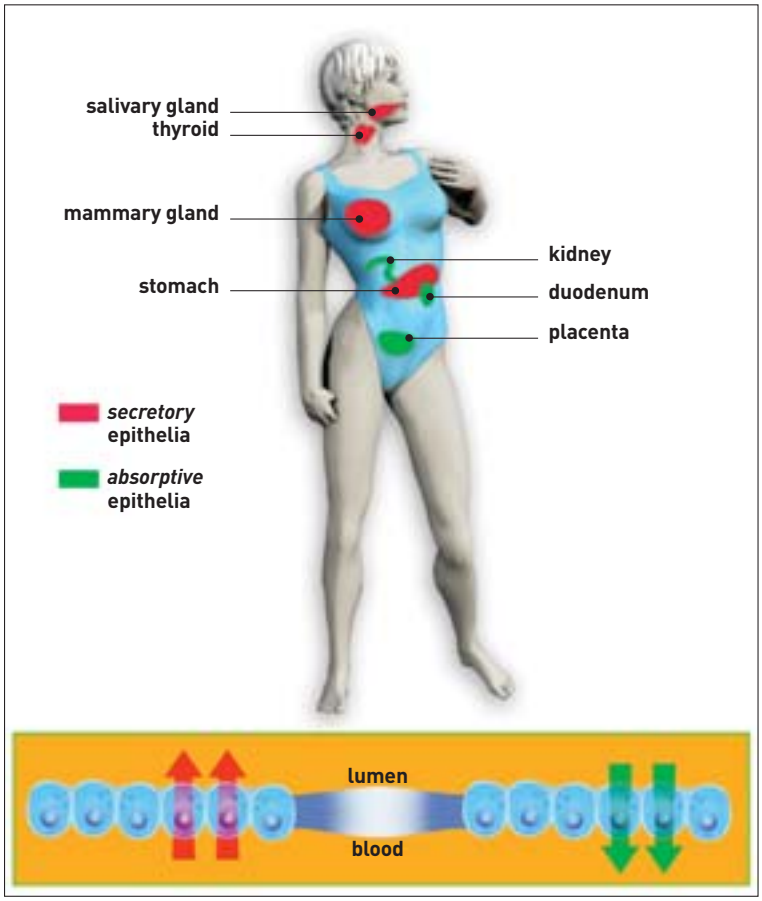


Figure 2.
Epithelia involved in iodine transfer in man. Depending on whether the active transport of iodide I^- is towards the blood or from the blood, the epithelia are defined as *absorptive* or *secretory*.

Iodine, which is naturally of low abundance, is a constituent of thyroid **hormones** in mammals. Iodides (I^-) are captured by the intestine, concentrated, and sequestered in **thyroid follicles** in the form of free iodide ion I^- and iodinated thyroglobulin, or finally redistributed to the fetus (*via* the placenta) or newborn infant (*via* the mammary glands) by different epithelial layers (Figure 2). The cellular accumulation of iodine is the first step in the active transport of iodide across the thyroid epithelium (Figure 3). It is catalysed by the sodium-iodide cotransporter (or NIS) localised in the basolateral membrane of the epithelial cells. Although it is highly selective for iodide relative to chloride, NIS transports technetium very efficiently as pertechnetate (TcO_4^-). This property is commonly used in functional exploration. NIS is strongly expressed in several other *secretory* epithelia (stomach, salivary glands, mammary glands in lactation). Its level of expression is lower in the testicles and ovaries. Its presence in these tissues deserves more thorough investigation in view of the possible **genotoxic** effects that iodine **radioisotopes** may have on **germ cells**. Lastly, the carriers that take iodine across the apical membrane of the *secretory* epithelia or those involved in its capture by *absorptive* epithelia (intestine or placenta) have not yet been formally identified and are the subject of active research.

> **Gérard Leblanc**, **Thierry Pourcher** and **Barbara Perron**
Life Sciences Division
University of Nice and
Joliot-Curie Department of Biology
Villefranche-sur-Mer (Alpes-Maritimes)

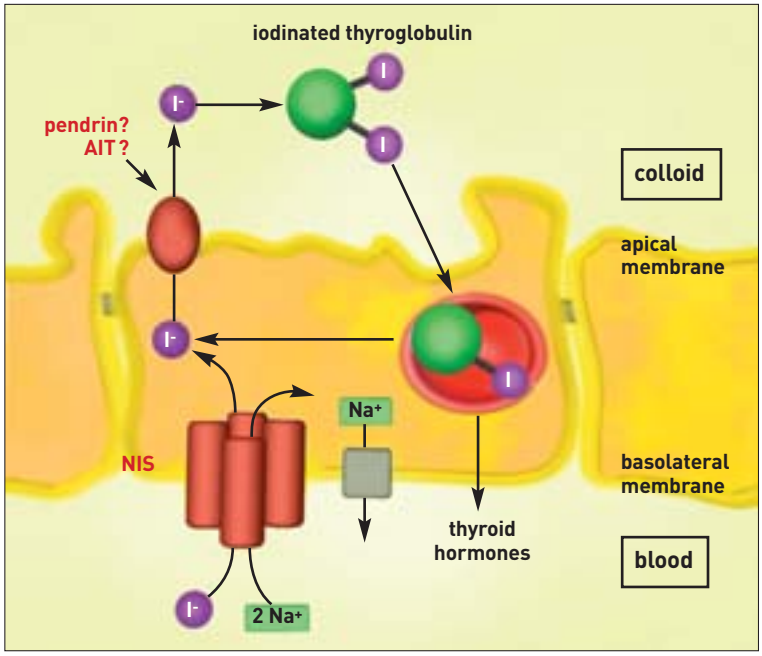
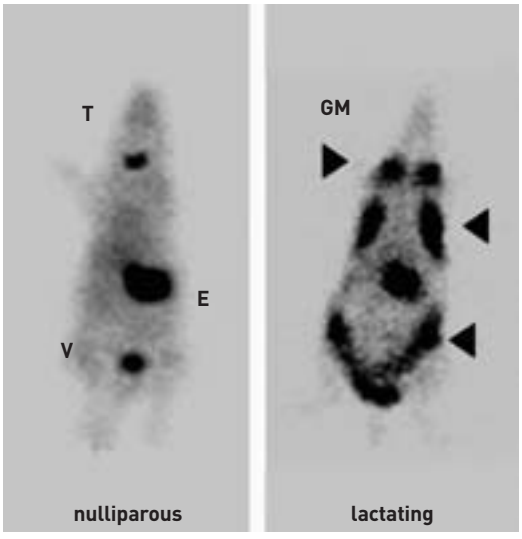


Figure 3.
Transport of iodide I^- by the thyroid epithelium. The iodide I^- is accumulated in the cells by the sodium-iodide (NIS) cotransporter located in the basolateral membrane. Pendrin and AIT (apical iodide transporter) are two apical membrane carriers that potentially handle the passive flow of iodide towards the follicular space.



N. Carrasco, A. Einstein College, New York, USA

Analysis by **scintigraphy** of the accumulation of $^{99m}TcO_4^-$ in different organs of a nulliparous and a lactating female rat (T stands for thyroid, E for stomach, V for bladder and GM for mammary glands).

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.

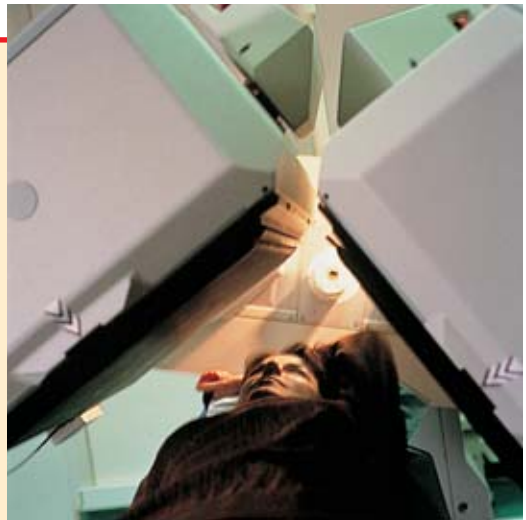
In the **Chernobyl accident** (Ukraine), which occurred in 1986, the total radioactivity dispersed into the atmosphere was of the order of 12 milliard milliard (10^{18}) becquerels over a period of 10 days. Three categories of radionuclides were disseminated. The first consisted of volatile fission products 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.

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.

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 (Ca^{2+}), potassium (K^{+}), sodium (Na^{+}), magnesium (Mg^{2+}) as cations, chloride (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 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[1] 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 hæmoglobin, 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 anæmia, 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 (hæmatopoiesis), is also a cause of anæmia. **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.

The CEA programme

The Nuclear Toxicology Programme was launched by CEA on October 1 2001 for a period of five years. It is a resolutely forward-looking programme comprising twelve projects that pool the expertise of physicians, biologists, chemists, physicists, etc. in the different Divisions of CEA. In 2003, this programme was opened up to France's other major public life science research bodies (Inserm, CNRS, Inra), and some projects are part of the European Commission's Sixth Framework Programme for Research and Technological Development (FPRTD).

The programme's central thrust is the *study of the biological effects of nuclear toxics*, i.e., all the compounds encountered in the nuclear industry that may have a chemical and (or) radiological toxicity towards living organisms. Its objectives are to study the toxicology of the materials used, in particular in nuclear **fuels**, to analyse the biological effects of **radionuclides** (naturally-occurring or artificial) that may be present in the environment, and to examine the effects of chemically toxic metals, particularly the **heavy metals**, used in nuclear research and industrial activities. For the radionuclides, the aim is to determine the potential health consequences of **exposure** to these materials and to make realistic estimates of the corresponding risks incurred.

The programme focuses on a range of **elements**: **carbon**, **cæsium**, **iodine**, **cobalt**, **strontium**, **selenium**, **technetium**, **tritium**, **americium**, **plutonium** and **uranium** for radiotoxicity, and **beryllium**, **boron**, **cadmium**, **lead** and again **cobalt** and **uranium** for chemical toxicity. One objective is to characterise their toxicity at the molecular and cellular level. Further elements will be examined as work proceeds.

The main research topics concern three types of mechanism:

- The mechanisms by which elements are transferred from the soil to plants, and transported from one cell to another.
- The mechanisms by which toxins accumulate in cell and tissue **compartments**.
- Specific detoxication mechanisms in bacteria, plants and animals.

In all cases, special emphasis is placed on work that makes it possible to compare the toxicity of different elements relative to a better known toxic chemical, such as cadmium or cobalt, and also, for as many elements as possible, work to compare chemical and radiological toxicity (cadmium, cobalt, etc.) when both stable and **radioactive** forms are present together. Special attention is paid to the toxicity of iodine[1], in particular to the mechanisms of its transport in the thyroid gland, and in other organs such as the mammary glands and the brain. To carry out this work, dedicated facilities are provided for the handling of elements of interest and the investigation of their effects on model organisms such as mice, plants and micro-organisms.

(1) Iodine, along with cæsium, was the most significant element released by the Chernobyl accident.