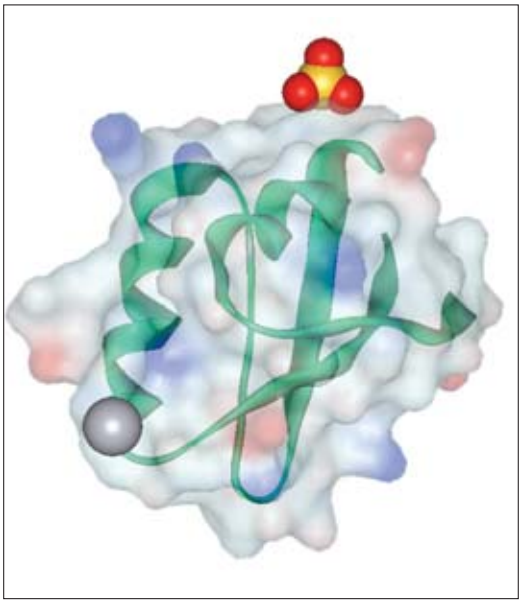
Uranium, better known each day

Studying mechanisms in the finest detail

Merely by its natural abundance in the environment and its presence in a normal diet (Box A, ***Natural and artificial radioactivity***), an average of 90 µg of uranium (U) can be found in the human body, mainly distributed in the bones (66%), liver (16%) and kidneys (8%). Only accidental situations can lead to an accumulation of uranium at levels liable to induce harmful effects. Even so, concern about its toxicity was voiced long ago: in 1826 the German chemist Leopold Gmelin conducted the first studies on urania (the old name for uranium oxide) and some fifteen **heavy metals** with a view to protecting miners. Uranium oxide had been isolated only about thirty years previously, and the French physicist Henri Becquerel was to discover its **radioactive** properties only seventy years later. Since then an efficient regulatory framework has been set in place, making it possible to respond rapidly, and on a scientific basis, to questions raised by public opinion during media scares such as that of the "Gulf War syndrome", blamed, despite the lack of firm evidence, on the military use of **depleted uranium**. However, a more and more detailed and quantified assessment of the risk is required, prompting new experiments to approach cellular and molecular mechanisms with ever greater resolution.



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Uranium is known to bind to the surface of certain proteins. This property is exploited in radiocrystallography for the determination of phases in protein crystals. Here, localisation of the uranium binding site (yellow) at the surface of the metallochaperone Hah1 (co-ordinates PDB 1FE4). About fifty structures in the Protein Data Bank were obtained in the presence of uranyl.

Harry Gruyaert/Magnum/Cogema

The first toxicological studies of uranium oxide were conducted more than a century and a half ago. Here, an underground mine of Cominak at Akouta, Niger.

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.

Tackling a rich and complex physicochemical field

All the **isotopes** of uranium have the same chemical toxicity, and a radiological toxicity that first depends on their radioactive **half life**: the longer this is, the weaker is the radioactivity and the lower the radiological toxicity (Box D, ***Radiological and chemical toxicity***). The ***in vivo*** behaviour of uranium and its toxicity result from its physical properties and its chemical reactivity. The kinetics of entry and distribution in the body will thus be quite different for a compound such as uranium oxide UO_2 of **valency** IV, insoluble at neutral **pH**, and for the uranyl ion UO_2^{2+} of valency VI, soluble in water (see *The fate of radionuclides in the body*). Generally, toxicity is linked to solubility and ease of entry into the bloodstream. But a soluble form is not necessarily a free form: the high reactivity of the uranyl ion with **oxyanions** (bicarbonate HCO_3^-, carboxylate $RCOO^-$, phosphoryl PO_3^{2-}…) means that it will not occur to any appreciable extent as a free form in biological media. The reactivity of uranyl towards the ionic groups of **proteins**, **phospholipids** and **nucleic acids** is also very high, a fact well known to biologists, who use uranyl acetate as a contrast agent in electron microscopy. Its ability to interact with **DNA**, which it shares with other metals such as nickel (Ni) and lead (Pb), may explain, more surely than its status as an **alpha emitter**, the **genotoxic** effect of depleted uranium described on **osteoblastic** cells or CHO(1) ***in vitro***. To make a finer investigation of the mechanisms governing the affinity and specificity of the association between the uranyl ion and its molecular targets, a collaboration has started between chemists and biologists at the CEA Marcoule Centre. Supported by **molecular modelling**, they are working to define a method for the identification of potential sites in proteins, for the eventual screening of a protein structure bank. An experimental validation of these targets, from both structural and energy viewpoints, will then widen the scope of empirical investigation, in particular to encompass electrostatic effects(2) (charge transfer, **polarisation**), which although most important are well described so far only in quantum chemistry(3).

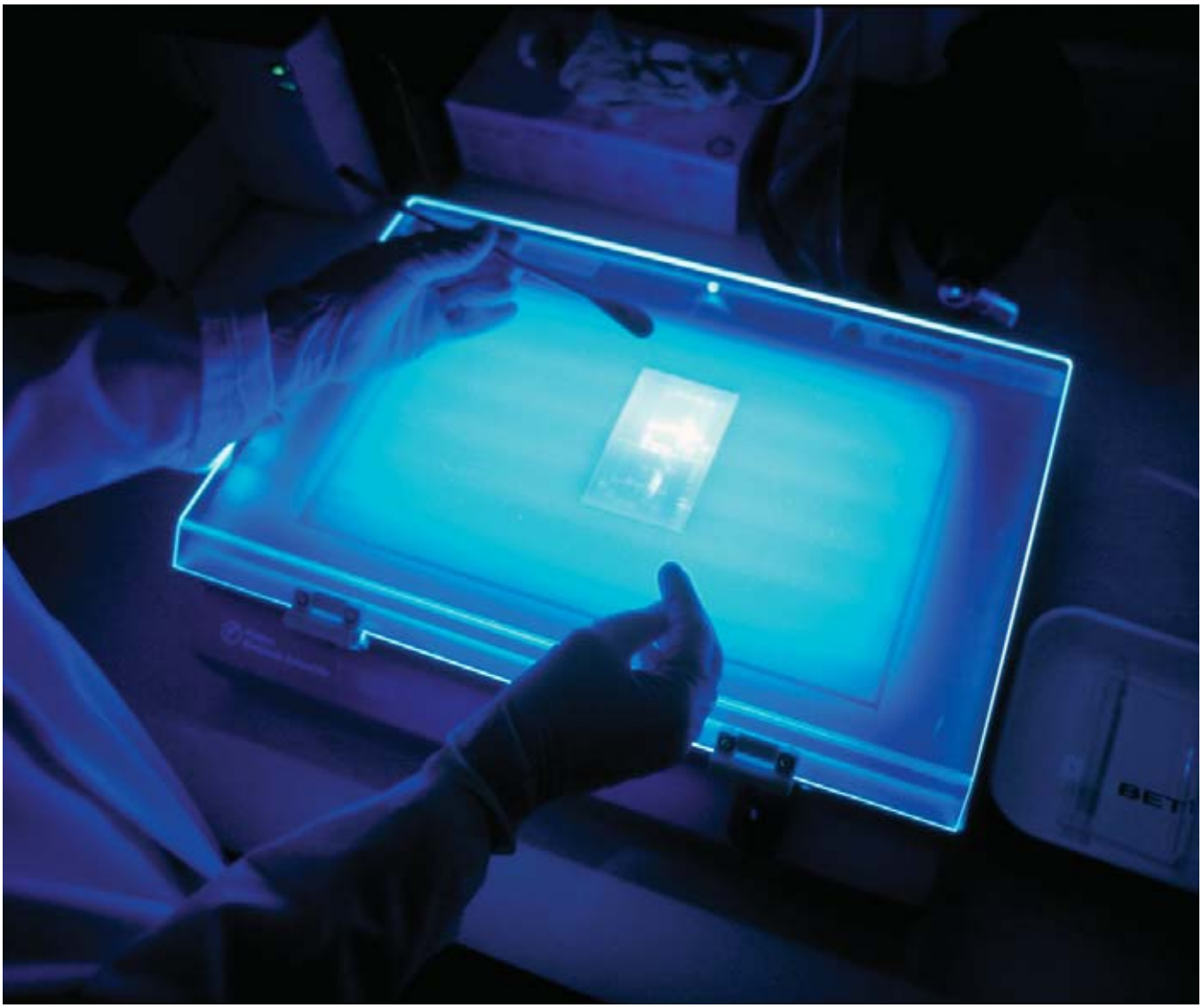
The biochemical mechanisms of nephrotoxicity

Only 0.2 to 2% of **ingested** uranium enters the bloodstream, where it occurs in the form of **complexes** in equilibrium: nearly 60% is bound to bicarbonates,

(1) CHO: Chinese Hamster Ovary cells. This cell model is widely used in molecular biology because it is easy to grow and transform genetically.

(2) Electrostatic: based on balanced electric charges that do not move (nil electric field).

(3) Quantum chemistry: a branch of chemistry (or physics) that deals with problems of chemistry using the theoretical models of quantum mechanics. The methods of quantum chemistry can be used to interpret chemical phenomena, reactions, and reaction mechanisms, and to predict the reactivity of certain chemical entities.



Cyrille Dupont/CEA

Visualisation of an agarose gel under a UV lamp for the study of DNA fragments at the CEA Marcoule Centre. All the tools of functional genomics and proteomics are mobilised to determine the biochemical pathways that are disturbed by toxics.

mainly as $UO_2(CO_3)_3^{4-}$, about 20% is associated on the surface of red cells, and some 20% is bound to **serum** proteins (albumin, **transferrin**, etc.). This distribution makes elimination by the kidneys efficient (60 to 80% of the uranium absorbed is excreted in the first 24 hours in the event of **intoxication**) because the uranium-bicarbonate complex passes easily through the **glomerular** filtration system, displacing the fraction reversibly bound to the proteins towards the filterable fraction. The combined effect of urinary acidification, which dissociates the complexes and the selective re-absorption of HCO_3^- in the **tubules** then prevents the uranium from returning to the bloodstream. When the uranyl concentration in the blood is high, disorders of the **proximal tubular** function appear. We note that the maximum admissible **dose** set by the **ICRP** is 3 µg/g of kidney tissue, making uranium much less intrinsically toxic for the kidney (nephrotoxic) than, say, chromium (Cr), cadmium (Cd) or mercury (Hg). Several mechanisms have been proposed to account for U toxicity. The metal may accumulate in the **epithelial** cells surrounding the tubule or may react chemically with their apical surface. Interference with the transport of ions and **metabolites** would then cause marked dysfunction and even cell death. The cell regeneration or division that can occur in response to these aggressions actually worsens the functional deficiency of the tubule. Alternatively, the uranyl ions may delay cell division, thereby amplifying cell damage.

A closer look at mechanisms of cytotoxicity

Excess uranium in urine causes its entry by endocytosis(4) into the epithelial cells. It concentrates in the lysosomes(5) until it **precipitates** as crystals of uranyl phosphate. These crystals are liable to damage cell structures, sometimes causing **lysis** and release into the urine of micro-calculi and of **enzymes** such as lactate deshydrogenase or N-acetyl-β-glucosaminidase, usual markers of tubule damage. This is an extreme scenario and the mechanisms now have to be studied

(4) Endocytosis: ingestion of matter by a cell through an invagination of the plasma membrane and its internalisation in a membrane-bound vesicle.

(5) Lysosome: cell organelle present in the **cytoplasm** of eukaryotic cells (that possess a nucleus), containing degradation **enzymes**. These organelles are specialised in the destruction of cell constituents.

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A new optoelectronic head fitted in the Kryptor controller for use in the screening of molecular targets of uranyl in human serum.

at more realistic doses, using methods capable of resolving the intracellular pathways (activation of MAPKs(6), transcription and post-transduction regulation(7)). The tools of **proteomics** and **genomics** are used in the framework of the Nuclear Toxicology Programme (box, *The CEA programme*) to analyse adaptation processes and responses, in particular to doses with no apparent effect on cells (< 0.1 µg/g of kidney tissue). The human cell models explored, until now of renal and pulmonary types, will later include bone and **germinal** types. The use of post-genomic approaches may eventually permit the identification of new markers of **exposure** or intoxication that are even more sensitive, or the prediction of individual risk factors.

> Éric Quéméneur
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(6) MAPKs: Mitogen-Activated Protein Kinases, extracellular substances that stimulate cell proliferation.

(7) **Transcription** is the process that permits the synthesis of a molecule of **RNA** from a DNA matrix by a mechanism that relies on the complementarity of **bases**, and the synthesis of proteins. **Translation** is the process by which the sequence of **nucleotides** of a molecule of **messenger RNA** directs the incorporation of **amino acids** in a protein.

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.

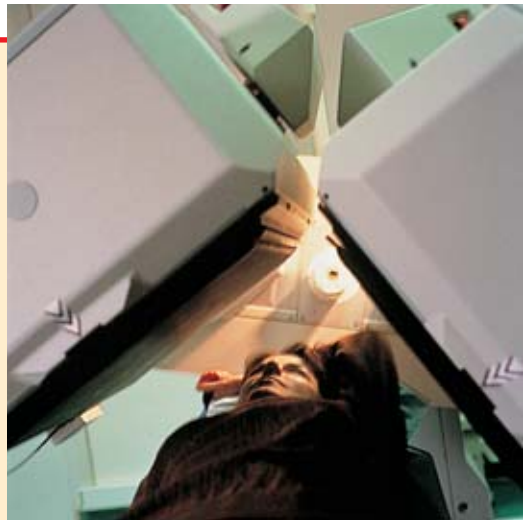
In the **Chernobyl accident** (Ukraine), which occurred in 1986, the total radioactivity dispersed into the atmosphere was of the order of 12 milliard milliard (10^{18}) becquerels over a period of 10 days. Three categories of radionuclides were disseminated. The first consisted of volatile fission products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

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.