Cadmium, a stress that builds up

Given its industrial utility (steels, anticorrosion treatment, cadmium-nickel (Cd-Ni) batteries, etc.), special attention is focused on this metal, which, in the nuclear field, is used for example as a neutron absorber in reactor operating devices.
The toxicity of cadmium has been known since the nineteenth century. It remained a minor risk until the exploitation of zinc (Zn), which is co-extracted with cadmium.
In Japan, the bone disease associated with cadmium (Cd) poisoning was known as "Itai! Itai!", literally "Ow! Ow!", as it was so painful. In Belgium, the inhabitants of a mining region were the victims of cadmium **intoxication**. In Japan, a variety of rice that accumulates **heavy metals** was implicated, whereas in Belgium the mining and smelting industry was the source of the pollution.

Circulation in the body and toxicity

Only 5% of the cadmium **ingested** is absorbed by the gastro-intestinal route. However, the lungs can absorb up to 50% in fumes. This is an important finding because cadmium is a soft metal that vaporises above 765 °C, and emits vapour below its boiling point. These temperatures are readily attained in industry, or even more simply at the incandescent end of a cigarette, which emits cadmium vapour – like rice and many other plants, tobacco accumulates certain heavy metals including cadmium.
Cadmium does not cross neither the **placental barrier** nor the **blood-brain barrier**. Its prime targets are the liver, bones and kidneys. After absorption, cadmium is first **metabolised** in the liver as a Cd^{2+}-glutathione **complex**(1) and then sent back into the circulation as a Cd^{2+}-metallothionein complex(2). This complex is re-absorbed by the kidneys where it is rapidly degraded. The Cd^{2+} ions thereby released in turn stimulate a new synthesis of metallothionein (MT) and, in particular in the cells of the **proximal tubule**, a dynamic equilibrium free Cd^{2+} ↔ Cd^{2+}-metallothionein is set up. The Cd^{2+}-metallothionein complex is not toxic, and the resistance of cells to Cd^{2+} ions, which are toxic, is directly proportional to the quantity of intracellular metallothionein. Thus in 2001, Jung D. Park *et al.* showed that a population of **transgenic** MT mice, which do not synthesise metallothionein, tolerates no more than a cumulative **dose** of 3 mg/kg of $CdCl_2$ and has an LD_{50} of 4.9 mg/kg, whereas a population of **wild phenotype** mice with normal metallothionein synthesis, can tolerate a cumulative dose of 23 mg/kg $CdCl_2$ and has an LD_{50} of 29.4 mg/kg. The synthesis of metallothionein induced by cadmium and its affinity for Cd^{2+} ions have an unexpected long-term **sequestration** effect, and so an accumulation of the Cd^{2+}-metallothionein complex occurs. The residence time of cadmium in humans is estimated at 15-20 years. During this time a Zn^{2+} stress, for example, can displace the Cd^{2+} from the Cd^{2+}-metallothionein complex. Consequently, any cadmium absorbed, even at a dose that is not toxic in the short term, will be stored and may become a threat if it builds up to high levels, especially in smokers. In 1999, Curtis D. Klaassen *et al.* estimated that 7% of the US population suffered from kidney problems due to chronic cadmium accumulation. Cadmium is evidently not a violent poison, except in case of massive accidental ingestion or **inhalation**. However its accumulation *via* metallothionein, in both animals and plants, potentiates its effects. Free Cd^{2+} ions are released, albeit in small amounts, but continuously.

An excellent model for study

This persistence of Cd^{2+} ions has prompted much recent research on the toxicity of cadmium at low doses and CEA is actively involved in that research *via* its nuclear toxicology programme (box). Cadmium is not a biological metal. It has few specific effects but tends to replace calcium, zinc, copper, etc. This opportunistic behaviour, which can cause severe physiological disorders, is common to many **exogenous** metals. Hence cadmium, the toxicity of which is well documented in physiopathological terms, is an excellent model to study the impact of certain metals on health and the environment.
Many questions now arise at the cell and molecular levels concerning the movement of cadmium, the **metabolisms** it disturbs, our means of resistance to it, and its molecular targets. For example, cadmium was

(1) Composed of three **amino acids** (glutamate, cysteine and glycine), glutathione is the main intracellular antioxidant. It plays a key role in the defence of the organism against certain toxic substances and radiation.

(2) Metallothionein is a low-molecular weight **protein** rich in cysteine. A specific arrangement of cysteine units allows it to bind heavy metals, such as cadmium.

Cells that adapt to cadmium

In 2002 CEA scientists demonstrated an important process of adaptation of cells to cadmium, in particular using global analysis tools from **genomics** (**DNA microarrays**, and **proteomics**). Observed in the yeast *Saccharomyces cerevisiae*, an organism used as a model of human cells, this process is a true detoxication process where cadmium, despite its high toxicity, can be trapped and eliminated by a living organism. This process might eventually be applied to soil depollution and the treatment of contaminated persons.
The trap is glutathione, a sulphur-containing molecule that forms a **complex** with cadmium which is then transported to the vacuole, a sort of cellular waste disposal area. Whereas sulphur is normally used for the synthesis of certain **proteins**, in the presence of cadmium it is essentially used to produce glutathione. Proteomic analysis has shown how the cell adapts to this decreased availability of sulphur, certain sulphur-rich proteins being replaced by proteins with the same function but poor in sulphur. In this way, nearly one third of the sulphur becomes available for glutathione synthesis and detoxication. An analysis of the **transcriptome** has shown that a transcription activator, Met4p, which plays a major role in the synthesis of sulphur-containing **amino acids**, co-ordinates glutathione synthesis and sulphur-saving mechanisms.

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classified as **carcinogenic** and **genotoxic** in 1993 by the *International Agency for Research on Cancer* (**IARC**). In a review published in 2000, Michael P. Waalkes suggests a mechanism of cancer formation through replacement of zinc, which is a physiological metal, by cadmium. However, the Zn/Cd cross-effects are often conflicting and cannot yet be interpreted in the state of current knowledge. To assess the cadmium risks and describe the cancer-forming mechanisms it will be necessary in particular to understand the effects of cadmium on **apoptosis**, or programmed cell death. Cadmium also has adverse effects on agricultural plants. M. Zafar Iqbal has reported, in the *Journal of the Society of Municipal Arborists* of Karachi, on the inability of certain seeds to germinate in cadmium-polluted soils. Conversely, in the journal *Nature*, James R. Larison *et al.* describe small highly resistant shrubs in the Colorado Rocky Mountains that accumulate cadmium in their berries. These berries are in turn eaten by wild birds, which develop an osteoporosis(3) that strongly resembles the disease "Itai Itai".

PhotoLink/PhotoDisc

Berries, such as those of certain shrubs that grow in Colorado, store cadmium. Wild birds that consume these berries develop a disease that resembles that observed in humans in Japan.

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(3) Osteoporosis is a disease characterised by lowered bone density and ill-formed bone tissue with consequent greater risk of fracture.

FOR FURTHER INFORMATION

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A Natural and artificial radioactivity

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

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

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

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

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

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

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

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

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

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

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

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

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

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

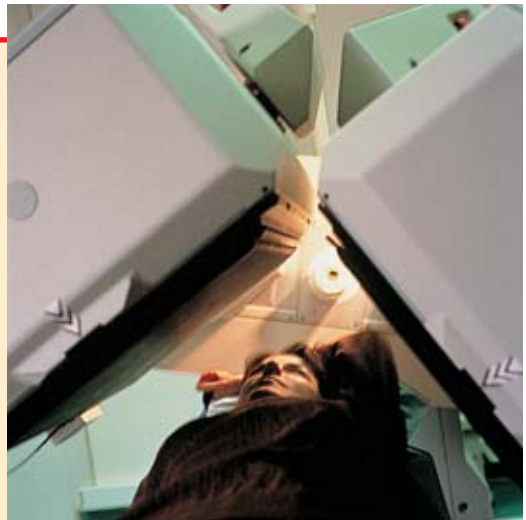
In the **Chernobyl accident** (Ukraine), which occurred in 1986, the total radioactivity dispersed into the atmosphere was of the order of 12 milliard milliard (10^{18}) becquerels over a period of 10 days. Three categories of radionuclides were disseminated. The first consisted of volatile fission products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

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

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

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

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



Laurence Médard/CEA

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

B Human exposure routes

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

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

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

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

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

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

F From rays to dose

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

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

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

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

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

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

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

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

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

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

Foulon/CEA

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

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

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

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

D Radiological and chemical toxicity

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

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

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

Cyrille Dupont/CEA

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