III. WHAT ARE THE EFFECTS ON HEALTH?

The objective of radiobiology and nuclear toxicology is to determine and elucidate the damaging effects of radionuclides and other toxics in order to forearm workers and the general population, and if necessary deal with the consequences of these effects (Chapter IV).

The most advanced branches of biotechnology have, in the field of functional genomics (see Chapter II), and of DNA microarrays, already allowed great progress to be made in the specific study of the most sensitive organs and tissues. The results will bring a better understanding of the modes of action of toxics at the molecular, cell and tissue levels, and in the organs and whole organism. Researchers are particularly interested in intra- and intercellular transfer and transport, and especially the molecular disorders that the toxics can cause in the cell's most important metabolic pathways.

On their own side, occupational medicine and biological medical laboratories, well developed long ago in the nuclear field, play an essential role in the monitoring and assessment of the individual exposure of workers and the prevention and management of accidental risk.

In normal situations, the important question is whether very low doses have any effect on health, given that no such effect, detrimental or beneficial, has yet been observed. To date no such effect can be demonstrated as a resultant of the elementary molecular mechanisms that are being gradually elucidated. The effects of high exposure levels, which differ widely according to whether or not they involve high dose rates, now better known and re-evaluated in the light of the latest advances made in radiobiology, have provided a basis for extremely cautious regulations.

Knowing the biological basis of dose assessment does not yet allow a simple and direct application to individual cases, or *a fortiori* to populations, even with the support of epidemiological studies. Until these two domains can be geared together, our task is to consolidate the scientific basis of the principles underpinning the international systems of protection from radionuclides and other toxic agents.

The effects on health of nuclear toxics range widely according to the cells, tissues and organs they preferentially affect. However, the lungs, bones, thyroid, kidneys, skin and the reproductive system are major targets, lending high priority to research on these organs.

Physiopathological **consequences** in cells and tissues

Radon and lung cancer: Research into specific features of radio-induced genetic alterations

The lungs are particularly exposed to toxics agents, for which inhalation is a preferred route of intake into the body. The effects of radon, which epidemiological surveys associate with excess lung cancer rates in uranium miners, are a major subject of study because this element is responsible for nearly 40% of the total exposure of the population. In this research, the rat is a valuable model for improving our understanding of the mechanisms of radon-induced cancer formation, and this model could help to characterise the molecular signature of a radio-induced cancer.

The example of **radon** illustrates the issues and difficulties of radiobiology: effects of low **doses**, existence of a threshold or not, effects of **dose rate** and duration of **exposure**. An omnipresent natural pollutant of telluric origin that emits **alpha radiation**, this gas, which accounts for 37% of the radiation doses received by the population, raises many questions. Its concentration, which is high in uranium mines, can also reach high values in certain dwellings.

Is its **inhalation** a risk, and if so above what level? **Epidemiological** studies have revealed excess lung cancer rates in miners, in particular of uranium. Other studies also suggest an association between lung cancer and domestic exposure, although no unequivocal correlation between observed effects and radon exposure levels has been established. Currently the risk of exposure at low doses is calculated by extrapolation of the data obtained among miners.

Can exposure and effects be more finely associated? Today we know that no signature demonstrating the radio-induced origin of a cancer can be found by classical methods. Clinical examination, histopathological analysis do not differentiate, for instance, between a "spontaneous" **adenocarcinoma** and one suspected of being radio-induced. Progress made in **genotoxicology** and in molecular biology could help to find a specific signature of the tumour etiology. For example, by focusing on well-defined **genes**, it has thus been shown in man lung cancer that the spectrum of **mutations** induced in the gene TP53 by benzo-a-pyrene, a constituent of cigarette smoke, differs very significantly from that induced by another genotoxic agent, aflatoxin, in liver cancer.

The role of oncogenes and tumour-suppressor genes

The genetic alterations detected in tumours can reflect their ætiology and the specific role of early events during their development. In solid tumours, these alterations are very numerous, the genes involved falling into two categories: oncogenes(1) and tumour suppressor genes(2). The first (proto-oncogenes) are abnormally **activated** or modified by mutation or structural rearrangement. The activation of an oncogene has three characteristics: (i) it leads to cell proliferation by altering normal cell cycle check points, (ii) the molecular alteration is targeted, specifically affecting a **nucleotide** or recombining two specific **DNA sequences**, and (iii) the alteration of a single **allele** is sufficient to confer growth advantage. This is therefore a *dominant* mutation at the cell level.

The function of the tumour-suppressor genes is to control the essential pathways of cell survival and proliferation. Their alteration also has three characteristics, which contrast with those of the

(1) Oncogene: gene that favours cell transformation and for that reason one of the many genes that contribute to the appearance of cancerous tumours.

(2) Tumour suppressor gene: gene that normally opposes the transformation of a normal cell into a cancer cell. It is mutated in cancer cells.

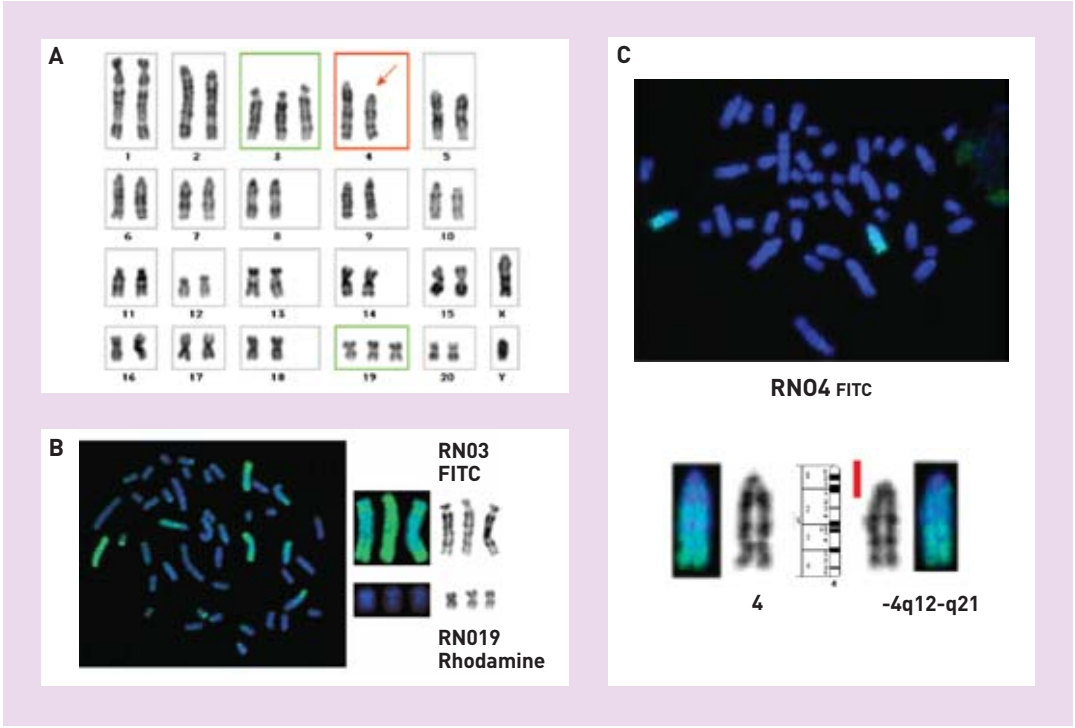


Figure 1.
Cytogenetic analysis of a radon-induced lung tumour in the rat (RN03: rat chromosome 3; 4q12: band 12 of the long arm (q) of chromosome 4; FITC and Rhodamine: fluorescent stains).
After enzyme treatment, the chromosomes from *in vitro* cultivated tumours in culture exhibit specific alternating dark and light bands ("banding"). The karyotype of this tumour reveals three copies of chromosomes 3 and 19 (A). Chromosome painting (FISH) of its metaphases with fluorescent probes specific to these chromosomes confirm 3 and 19 trisomy. The size and banding of the two chromosomes 4 (A, C) are slightly different. The hybridisation of the chromosomes of this tumour with a probe specific to chromosome 4 shows that it is indeed a pair of chromosomes 4 one copy of which presents a deletion.

proto-oncogenes but have the same consequences: (i) the molecular alteration is not targeted (a gene can be inactivated in many ways), (ii) it leads to a functional loss, most often a loss of control concerning proliferation or cell adhesion, and (iii) the function of the coded **protein** is generally lost only if both alleles are affected. The mutation is therefore *recessive* at the cell level.
At the cytogenetic and molecular levels, the regions of the **genome** that are lost or gained in the tumours are not strictly limited to the gene but could overlap thousands of genes located in the same area. The difficulty is identifying those that are directly related to the carcigogenesis process. After that, it is then necessary to determine whether the way of gene alteration in radio-induced cancers displays special features, and whether one or more of such features can convincingly serve as a signature of radiation origin. The identification of such a signature would of course have far-reaching implications.

Characterisation of genetic alterations in induced tumours in the rat

The rat constitutes a useful model for the short and long-term study of lung **carcinogenesis** after radon inhalation. The study of the cytogenetic and molecular alterations in these tumours should improve our understanding of the mechanisms of carcinogenesis radio-induced by radon, and ultimately make it possible to identify biological tools that will reliably distinguish between radio-induced and non-radio-induced tumours.

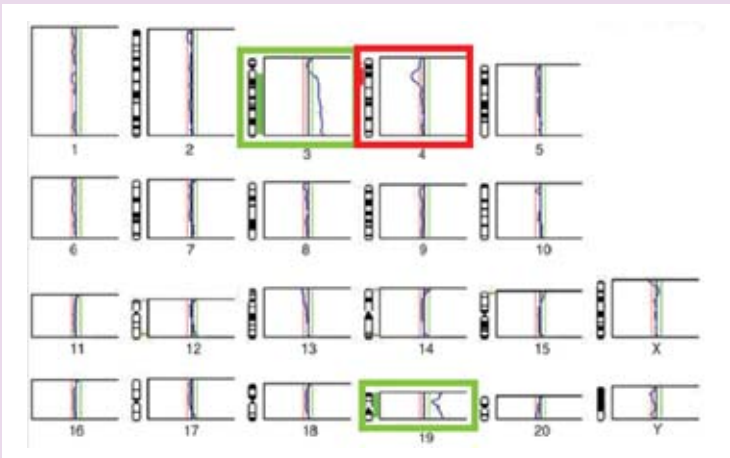


Figure 2.
CGH diagram of the radon-induced lung tumour the karyotype of which is presented in Figure 1. In CGH, the DNA of normal and cancerous cells is marked by red and green fluorochromes respectively. The overall chromosome stain colour, hybridised in the same amounts on normal metaphases, depends on the balance normal/tumour DNA. Deletions will cause a reduction of the green-marked probe and the chromosome segment of the normal metaphase will be too red. Conversely, it will be too green if tumoral DNA has excess material. These variations are computer-analysed to plot fluorescence curves along each chromosome.
The diagram shows a close concordance with the karyotype analysis. The gains of chromosomes 3 and 19 induce a deviation to the right; the loss of a part of chromosome 4 a deviation to the left.

The first aim was to develop methods of global analysis of the rat genome to identify the **chromosomal** regions gained or lost, and then develop a targeted approach to identify the genes involved and their ways of activation or **repression**.

Global genome analysis

The global study of chromosomal rearrangements was carried out by classical cytogenetics by analysing the **karyotype** of tumour cells (Figure 1A); these anomalies were then confirmed or detailed by *in situ* hybridisation using specific chromosome probes (Figures 1B and C).
CEA scientists have adapted to the rat a second global analysis method previously used to analyse the human genome, namely comparative genomic hybridisation (CGH), based on the differential hybridisation of a mixture of DNA from normal and tumour cells. It can determine, in one step, all the gains and losses of genetic material, but gives no information on the alteration or rearrangement of chromosomes that led to them (Figure 2).
Rat and mouse karyotypes had been compared, first to sort each chromosome and prepare specific probes for *in situ* hybridisation, and second to improve knowledge of the rat genome. This was a crucial aid to interpreting abnormalities detected by the global approaches and the search for candidate genes.
Moreover, as the correspondence between the mouse and the human genome is well established, data obtained on rat tumours could be compared with those obtained in human tumours. Candidate genes could then be listed to continue the characterisation of the tumours at the gene level by classical molecular biology methods.
In a series of 16 tumours induced by radon inhaleation studied by cytogenetics and CGH, it was demonstrated in early 2003 that some anomalies were recurrent. In addition, genetic anomalies observed in rat tumours were found to be homologous to frequently altered chromosome regions (30 - 80%) in human lung cancer. Among the candidate tumour suppressor genes or proto-oncogenes involved were MYC, MET, p16, p15, FHIT and RB1; others remain to be identified. These encouraging results make it possible, besides continuing the global analysis, to draw up a more narrowly targeted strategy to study the genes potentially associated with the radon-induced lung transformation process. In addition, the discernable similarities between the genes altered in lung cancer in humans and rats suggest that the rat model can be extrapolated to man and could be useful for the study of the early genetic alterations associated with lung carcinigenesis.

CEA/DAM/Idf

Laboratory study of the **metabolism** of rodents exposed to radionuclides.

Targeted analysis: searching for mutations of the gene TP53

Parallel to the global analysis of the cytogenetic alterations, targeted approaches have been developed to characterise the radio-induced mutations.
Researchers first of all analysed the tumour suppressor gene TP53, which is very often altered in solid tumours. Its activation takes place by mutation of an allele and loss of the **wild** type allele. It is thus an ideal target to determine whether there is a specific feature in the spectrum of the radio-induced mutations. The mutations of the gene TP53 were analysed by **sequencing** cDNA obtained from radon-induced rat tumours. Out of 39 lung tumours, 8 mutations were detected, 7 of which were deletions. In all cases the deletions were losses of more than two pairs of **bases**.
What is remarkable is note directly the frequency of mutations, but the type of alterations, i.e., deletions. The frequency of deletions is much higher than that observed in spontaneous occurring tumours or in those induced by other **mutagens**. In addition, within the deletions, losses of two or more nucleotides are much more frequent in radon-induced tumours in the rat than in human lung tumours. It was also shown, in collaboration with Bernard Malfoy at the Curie Institute, that a high frequency of deletions in the gene TP53 occurred in a series of human tumours induced by radiotherapy.

O. Soulié/IRSN/2003

Mobile laboratory of the nuclear radioprotection and safety institute used for radon measurement campaigns, here at Meymac (Corrèze).

Does the deletion of more than two base pairs indicate radio-induction of a tumour?

In addition to revealing, for the first time, a specific feature of radio-induced genetic alterations, these results cast some light on the mechanisms of carcinogenesis induced by radiation. Point mutations and deletions of a base preferentially indicate errors in the repair of altered bases or in replication, whereas deletions of more than one base are more likely the result of double strand **DNA** breaks.

Thus it is not very realistic to expect to obtain a true signature of radiation damage by the analysis of mutations. It is rather the nature of the damage, in particular the observation of a series of deletions of more than two pairs of bases, that may be suggestive of radio-induction of a tumour. If this is so, then this type of alteration should not be limited to the gene TP53 but should also be found in other suppressor genes inactivated by mutation, such as p16 for example. Work on radio-induced tumours in man and animals is in progress to follow this up.

Researchers are developing other models of radio-induced lung tumours in the rat: tumours induced by inhalation of plutonium and **osteosarcomas** induced by injections of plutonium. The analysis of these tumours will enable them to determine whether these first conclusions on radio-induced tumours are generalisable to all tumours, all types of irradiation, all contamination routes and finally all species.

> **Sylvie Chevillard** and **Marie-Noëlle Guilly**
Life Sciences Division
CEA Fontenay-aux-Roses Centre

A Natural and artificial radioactivity

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

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

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

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

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

Uranium-238 is an alpha emitter with a half life of **4.47 thousand million years**. It has thirteen main alpha-, beta- and gamma-emitting radioactive descendants, including **radon-222** (**3.82 days**) and **uranium-234** (**0.246 million years**). Uranium-238 and its two descendants **thorium-234** (**24.1 days**) and **protactinium-234m**(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.

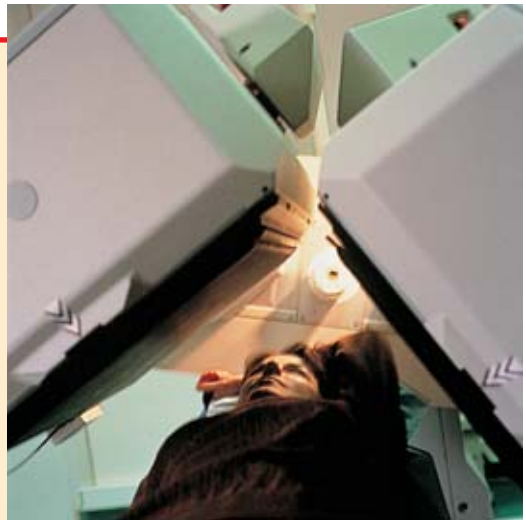
In the **Chernobyl accident** (Ukraine), which occurred in 1986, the total radioactivity dispersed into the atmosphere was of the order of 12 milliard milliard (10^{18}) becquerels over a period of 10 days. Three categories of radionuclides were disseminated. The first consisted of volatile fission products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