RESEARCH PERSPECTIVES

Whether in the research that has been continuing ever since nuclear energy was first applied to electricity production, defence and medicine, or in programmes launched more recently, radiotoxicology, and more generally nuclear toxicology, have proved to be markedly multidisciplinary areas, as shown in the preceding chapters.

From the health standpoint, it is increasingly obvious that progress in the elucidation of biological processes will only lead to significant advances in protection, and increased capacity to deal with incidental or accidental risks, through ever closer collaboration among researchers – physicists, chemists, or biologists –, healthcare professionals and engineers.

Internationally, the evolution of the concepts governing protection has generated a dual viewpoint: protection from radioactivity and chemicals, and protection of people and the environment, or more exactly non-human species. In line with this trend, The IAEA and the ICRP propose working documents for open discussion, and already the European directives on water, air and soil propose joint management of radiological and chemical risks.

From a strictly biological standpoint, one of the difficulties in devising a consistent protection system arises from the scarcity of reported results on the adverse effects of low doses and low concentrations of toxics common in situations of chronic exposure.

It was in this context that CEA launched its Nuclear Toxicology Programme on themes concerning nuclear toxics, in particular on the mechanisms by which these toxics are transferred in the environment and transported in living organisms, from plants to mammals. The approach adopted was analogous to that undertaken in radiobiology with the setting up in 1994 of a network of laboratories to pool the expertise of all the relevant research bodies. Just as with radiobiology, this research is closely linked to genetics, and medical and biological research, with all the possibilities offered in particular by global analysis methods and the use of model organisms.

The research conducted in the framework of the CEA programme, in collaboration with the other French public research bodies and other research teams in Europe and elsewhere in the world, can thus be broad enough in scope to address the implications for human health and environmental quality of the use of nuclear technology. The objectives are multiple, from the elucidation of the biological mechanisms that guide the behaviour of elements in the biosphere, to the design of prevention and treatment methods. The results of this work should also help to strengthen the scientific basis of protection.

Future trends in the protection against the effects on health of radiological and/or chemical toxicity will certainly be based on improved knowledge of specific biological mechanisms and individual sensitivity. Progress in these areas will most likely be made at the interfaces between research, healthcare and biomedical monitoring.

The **effects on health** of radiological and chemical toxicity

A concern shared by scientific research, medicine and engineering

Overall exposure to **radioactivity** derived from human activities has diminished in both the workplace and among the general public. Yet somewhat paradoxically, great concern is felt about the delayed effects of **radiation**, in particular cancer formation. Compliance with **dose limits** or comparison with **natural radiation** do not sufficiently reassure the population. In parallel, in nuclear research and industrial activity, processes are changing and the dismantling of old plant, which is only just beginning, heralds potential exposure to **elements**, both radioactive and stable, in physicochemical forms (**aerosols**, solubility) hitherto seldom encountered. It is thus necessary to study the biological behaviour of certain **isotopes** and **complexes**, and organic compounds of ranging forms. It is also necessary to verify that extrapolation from data concerning **radionuclides** with known biological behaviour, or reference to chemical analogues, are sufficient to estimate biological effects and hazards.

A necessary interaction

To answer the public's questions about the potential effects of nuclear plants and identify new situations of exposure that require specific analysis, interaction is necessary between occupational health and safety services, physicians and pharmacists responsible for

A. Gonin/CEA

Dismantling the Brennilis power station (Finistère). The disassembly of old plant can expose workers to elements in unfamiliar physicochemical forms.

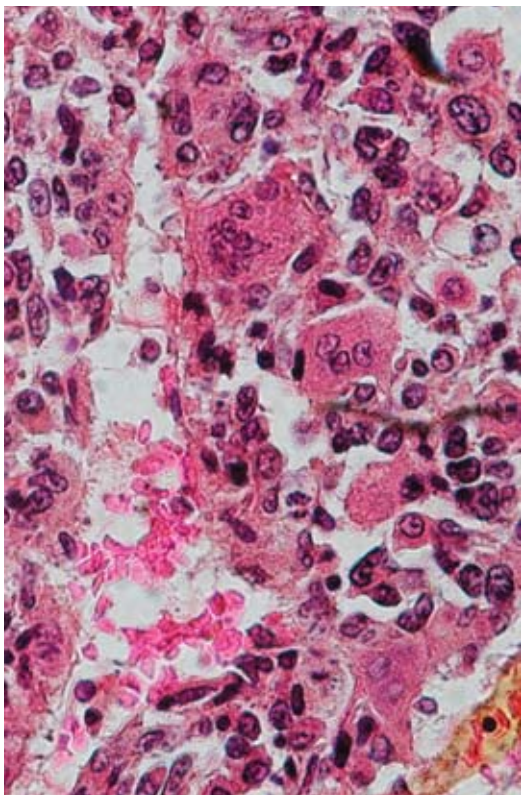
occupational medicine, engineers, physicists and chemists who develop new research or industrial processes, and research biologists. The latter focus on elucidating the mechanisms of action of elements, both radioactive and stable, and also develop diagnostic and therapeutic methods.

The role of Carmin

At CEA – where historically the radiological aspect has been always central – the Carmin unit (unit for the analysis of biological research applications in occupational medicine and their interface with the effects of radiological and/or chemical toxicity) exemplifies this interaction. This co-ordination unit is concerned with the evolution of research in biology and of concepts in research and industry. Its job is to follow research on the effects of radiological and chemical toxicity and its implications for biological monitoring, prevention and protection. One aim is to identify, jointly with physicians, biologists, researchers and engineers, the situations in which **dosimetric** calculation is not sufficient to predict health risks, and to propose studies to find answers to the following questions: What is the nature of the hazard? What means of prevention are there? What treatments may need to be developed to forestall any adverse effects of exposure?

Radioprotection, a efficient system

The evolution of the system of radioprotection clearly attests its efficiency. Since the **ICRP** was set up (see *How is the ICRP keeping pace with change*?), successive recommendations based on the analysis of clinical observations and experimental studies have eliminated the adverse effects of high doses and limited excess **stochastic effects** to a level such that it is practically impossible to discern it against the natural "background noise".



CEA

Pulmonary metastasis of **osteosarcoma** induced in the rat after systematic plutonium contamination. Radioprotection has eliminated adverse effects of high doses of irradiation.

The **effective dose** is the parameter that makes it possible to record and compare human irradiation from both external and internal sources. This dose, which ultimately represents the risk of developing fatal cancer and transmitting a hereditary radio-induced **mutation**, was established essentially from the follow-up of groups exposed to whole-body **external irradiation**. However, there are situations in which the use of the effective dose does not suffice to account for an effect or a health hazard.

Risks of misleading interpretation

A few recent examples show that the exclusive use of the effective dose, in particular when deriving from heterogeneous overexposure, brings with it a risk of misleading interpretation outside the strict biological or medical context. The inaccurate use of direct calculation of effective dose, from the activity in **becquerels** (Bq), leads to errors in evaluating the biological significance of the dose and in the interpretation in terms of incurred risk. Experience shows that medical and biological analysis *must* be allied to sound radioprotection analysis.

The example of Chernobyl

The Chernobyl accident is a good illustration of the dangers of wrong interpretation. During the days and weeks after the accident, large quantities of radionuclides were dispersed in the atmosphere and subsequently into water and the food chain. Initially, the main fear was of radio-induced leukemia, known to appear with the shortest latency, among the emergency firefighters and the most heavily exposed members of the local population. Yet it was thyroid cancer, not leukemia, that appeared 3 to 4 years after the accident in children living in the most heavily contaminated areas. Although the **carcinogenic** effect of thyroid irradiation during childhood was well known, knowledge of the magnitude of the thyroid doses was imprecise, which doses were made larger by the insufficient daily supply of stable iodine to these children. In this accident situation, numerous combined factors resulted in an under-estimation of the dose: the quantities of iodine radio-isotopes dispersed, the heterogeneity of the dispersion and the preventive supply of stable iodine, the insufficiency of which allowed an uptake of radio-active iodine by the thyroid higher than expected. In addition, direct measurements of individual **contamination** by iodine-131 were faisable and carried out over a short period of a few weeks on a limited number of persons. Overall, the under-estimation of locally-produced milk consumption and of the previous deficiency of stable iodine, heterogeneity in the preventive treatment given, and an initial under-evaluation of the **source term** resulted in an under-estimation of the thyroid cancer hazard in children, in particular in the regions of Belarus, where both the contamination and the previous deficiency of stable iodine were most marked.

In the rest of Europe, the contamination was much lower, and the **epidemiological** studies conducted by the European Community and **IARC** (International Agency for Research on Cancer, a body set up under the ægis of the **WHO**), show no increase in risk. In France, in particular, the consequences of the accident were of a quite different order. The conditions of exposure by **inhalation** and **ingestion** of food contaminated by iodine radio-isotopes was responsible for an irradiation of the thyroid at least 100 times weaker than in Belarus. The difference in exposure levels is illustrated by the maximum concentrations of radioactive iodine in cow's milk – about 500 Bq/L in France against 10^6 Bq/L in Belarus –, which takes the calculated doses in our country below the values at which any risk of cancer could be quantified even in young children. In these conditions, only a specialised medical assessment might, in individual cases, be able to establish whether a cancer of the thyroid could have been caused or facilited by the Chernobyl accident, based on clinical antecedents and age, and dietary patterns during the weeks following the accident.

Public disquiet is no more rational for other radionuclides such as radiocæsium. Its detection in the human body, from the lowest concentration, does not necessarily mean that it is responsible for various adverse effects on health. Similarly, naturally-occurring or **depleted uranium** is still presented essentially as a **radiotoxic** element, despite abundant scientific information relayed by NATO, the UN and the European Community. It is still difficult to convince people that although uranium is a radioactive element, the toxic effects of depleted or naturally-occurring uranium are mainly due to its chemical properties. In other words, the concentrations of these forms of uranium that would have radiological effects are much higher than those at which they are chemically toxic.

French nuclear test veterans

Between 1960 and 1996, France carried out nuclear weapon tests, first atmospheric and then underground. More than 100,000 workers participated in their preparation and in the subsequent collection and processing of test data. Before the tests, a dosimetric monitoring system for personnel and the environment was put in place, supported by data acquired over the previous fifteen years by the other nuclear powers. The results of individual monitoring carried out by CEA showed the cumulative doses to be low, and below the levels known to cause excess cancer prevalence. Today, those involved in the tests are in the age groups in which the background frequency of cancer increases, and in which many health disorders develop. Many of these persons are now demanding radiobiological tests to find evidence for an early occupational irradiation.

Although there are tests that can identify irradiation that occurred several years or decades previously, their interpretation is delicate and requires a response curve for a reference population. These tests can, according to the case, attest a whole-body or local irradiation, and were devised for use mainly after single acute homogeneous irradiation, with a sensitivity threshold of about 0.2-0.3 **gray** (Gy). They are generally not validated for heterogeneous, repeated or chronic irradiation, more representative of occupational exposure patterns. Specificity as a retrospective dosimetric indicator varies from one test to another, and the test results lump all irradiation effects regardless of origin (occupational, medical and natural), and sometimes also exposure to other agents such as ultraviolet radiation. Repeated radiological examinations, not to mention chemotherapy or radiotherapy, can mask the imprint of earlier occupation exposure. In view of the difficulties met in interpreting the results, only on the basis of a combined analysis of individual medical and dosimetric files can the most appropriate tests be properly selected, according to the context, among the many that are available.

The case of Tokai Mura

The accident of Tokai Mura that occurred in Japan in 1999 illustrates in another way the difficulty met in assessing a type of radiation that is fortunately most uncommon. This was a criticality(1) accident due to the non-application of procedures designed to guarantee safety and radioprotection, and an inadequate knowledge of the often lethal consequences of such an accident. Although the accident was due to nuclear materials, here uranium-235, the health effects were caused by *external irradiation*. However, the initial information transmitted was imprecise, leading the emergency medical teams to believe that the three victims were *contaminated* with uranium, which could have oriented the emergency medical intervention in quite the wrong direction.

Two completely different situations

The situations with which physicians and biologists are faced are radically different according to whether the exposure in question is *usual* or *accidental*. In the first case, whether the exposure in occupational or domestic, the level is low, of the same order as natural radiation exposure, and often below the detection thresholds. There is no observable reproducible biological effect that indicates that a reduction of exposure is accompanied by a reduction of risk.

In the second case, which implies a possible risk of high-level exposure, it is necessary to have sufficient knowledge of the consequences to act preventively and protect persons involved. One issue is that of knowing what research areas should be developed for prevention, diagnosis and treatment, and what adverse effects the proposed treatments may entail (for example, the depletion of certain vital elements).

Underlying biological issues

How can we estimate the nature and level of risk after exposure to chemical and radiological toxic elements? The answer to this question is especially elusive for chronic exposure to low doses or concentrations, for multiple exposure, and when the level of each exposure is close to average environmental levels.

Since it is impossible to describe all the situations of

(1) On this subject, see *Clefs CEA* No. 45, p. 46.

L. Médard/CEA

Preparation in a hood under argon of air-sensitive proteins for the study of their response to oxidative stress.

exposure affecting people and the **biosphere**, it is necessary to identify those for which more thorough analysis is justified. For certain sources of exposure, human and experimental data are insufficient or even absent, whether the toxicity of the physicochemical forms involved is radiological or chemical. This is the case for certain **lanthanides**, for example.

General and specific mechanisms

Generally, it is necessary to understand elementary biological mechanisms to be able to establish a scientific basis for protection policy, and to develop the means to compare radiological and chemical effects in the nuclear field. We already know that although some of these mechanisms are common, others are more specific to the causal agent. Although many **DNA** lesions are comparable whatever their cause (radiation, **oxidative stress**, see box), others are specific, such as thymine dimers, which appear after exposure to ultraviolet radiation, or damage to a particular **base** by some chemical agent. Similarly, a greater proportion of double-strand DNA breaks is observed in damage caused by **ionising radiation**. This is one reason why radiobiological research focuses first on DNA damage and its repair (sometimes faulty and **mutagenic**). Even so, the repair mechanisms only take into account the *nature* of the damage, and the different types of stress (irradiation or chemicals) and their response patterns still need to be compared.

The biological behaviour of radionuclides, in particular their transport in the body, is first of all guided by their chemical properties. Accumulation in certain cell types and cell **compartments** can account for local toxicity, which can be either radiological or chemical. The bones and liver retain both **alpha emitters** such as plutonium or americium and **beta/gamma** emitters such as strontium. For long-lived radionuclides such as technetium-99, toxicity is primarily chemical. For others, such as neptunium-237, chemical and radiological toxicity have to be considered together.

How are cause and effect linked?

Exactly how and to what degree a cause and an effect are linked is a recurrent question. When the expected effect of irradiation is the appearance of cancers, the quantitative estimation of the risk is based on numerous relationships between dose and excess cancer rates, excess rates at low doses being extrapolated from those observed at high doses. Although at the lowest levels of irradiation the elementary effects (for example the number of DNA lesions) mostly follow a relationship that is linear with no threshold, the resultant of these effects and the appearance of pathological effects are generally not linearly related to dose. The *resultant* integrates processes that each follow dose-effect relationships of different nature and form, ranging from cell **apoptosis**, to the **bystander effect** (damage *indirectly* radio-induced) and probably also adaptative response(2) effects, although the results

(2) Adaptative response. In certain biological systems, when a high dose of radiation (2 Gy) has been preceded by a weak dose of radiation (~0.1 Gy) during the previous 24 to 48 hours, the biological effects are milder than when no prior low dose of radiation has been received.

obtained for this last process cannot yet be generalised. Dose-effect curves have been plotted for chemical **genotoxic agents**. The limits are defined for each form according to the detectable effects.
In both cases, as a scientifically-based direct relationship with the appearance of a cancer or other late-onset disease cannot be firmly established, safety factors (of the order of 10 to 100), either for concentration (chemical), or for **dose rate** (radiological) have been adopted.
The physiological approach is becoming increasingly important. This approach is complex because the human body evolves continuously from conception to senescence. Two major questions arise: that of the biological significance of measurements, calculations and dosimetric models, and that of the relations of causality, in particular at low exposure levels, between exposure to a radiotoxic and (or) chemotoxic agent, an the risk of subsequent disease, e.g., cancer.

Radiobiology: methods for a global approach

The methods recently developed in biology, supported by genetics and constantly advancing knowledge of the functions of **genes** and genetic and **metabolic** regulation in cells and tissues, have allowed the development of radiobiology methods for a *global approach* to study the cell's biological response at the levels of the **transcriptome**, the **proteome** and the **metabolome**.
It is thus possible, for very low exposures, to carry out a simultaneous analysis of all or part of the genes or **proteins** of a cell and so determine what genes or families of genes are involved in the stress response. This approach has already yielded results with the mammalian cells and single-cell organisms such as yeasts.
It will also be possible to identify genes that are expressed differently according to the individual, to evaluate the influence of genetic susceptibility in the occurrence of damage, and eventually establish radiosensitivity profiles and more generally, individual sensitivities. This approach will also help to provide an explanation for effects such as hypersensitivity to high doses, which results in the appearance of "second cancers" in up to 10 to 15% of cases in radiotherapy. In the area of medical irradiation, the objective is to reduce the level of irradiation at constant quality of care, the benefit/risk ratio remaining the essential criterion.

"Elegant" means of prevention and treatment

Exposure limits are now sufficiently low for scientific advance not to prompt an escalation of protective measures based on such limits. The dose limit for the

The cellular mechanism of oxidative stress surveillance unravelled

An essential part of the cell response to **oxidants**, the mechanism by which the cell detects and reacts to the presence of oxidants was discovered at the end of 2002 by researchers at CEA. Once again, they made use of the yeast single-celled eukaryotic model *Saccharomyces cerevisiae*. They believe that the surveillance mechanism utilized by yeast has been conserved during evolution, especially in man.
Oxygen-derived species such as hydrogen peroxide are implicated in the ageing process and in the genesis of cancers. They also contribute directly or indirectly to the toxicity of many toxic chemicals and of harmful **radiations**. Scientists at CEA have discovered the cellular sensor system detecting hydrogen peroxide, an actual surveillance and alert system triggered by the presence of elevated concentrations of hydrogen peroxide in the cell. This system comprises Orp1, the actual **redox** sensor, and Yap1, the **transcriptional** regulator **activated** by Orp1 when oxidants are being detected. When activated by Orp1, Yap1 orchestrates a protective cellular response towards oxidants that include the production of anti-oxidants. Orp1, for Oxidant Receptor Peroxidase 1 is also known as Gpx3 and belongs to a major family of anti-oxidants, the glutathione peroxidases. This is itself a remarkable finding because it shows that **proteins** responsible for eliminating oxidants also regulate their own expression.
By a redox process, Orp1 transmits the signal to Yap1. The activity of the two proteins is thus regulated by oxidation, and the signal transmitted corresponds to an oxidation of Yap1 by Orp1. Thus oxidation of proteins, till now only considered as a harmful process, appears to have a regulatory role, adjusting the activity of specific proteins and enabling the cell to adapt to the presence of oxidants.

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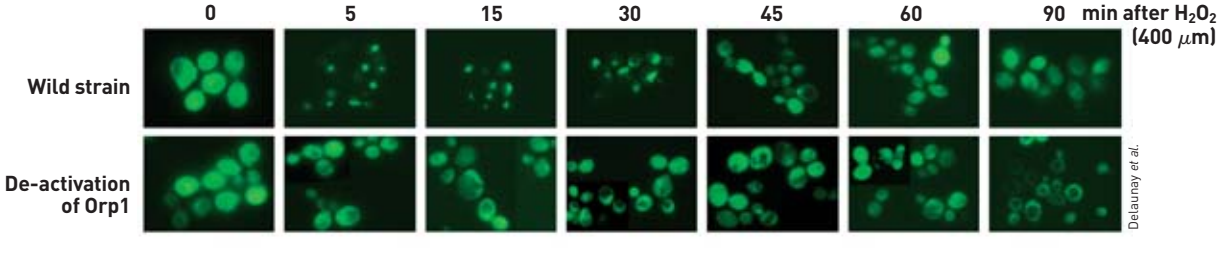

Activation of the regulator Yap1 by hydrogen peroxide (H_2O_2) dependent on the presence of detector Orp1. In the **wild** strain (top microscope images), Yap1 (green) is activated, as shown by its accumulation in the nucleus, visible 5 minutes after treatment. With no activation by the detector Orp1 (bottom images), Yap1 is no longer activated by H_2O_2 and remains **cytoplasmic**.

F. Foulon/CEA

Remote handling at the Atalante laboratory, at the CEA Marcoule Centre. The development of new processes can lead to new types of exposure to nuclear toxins.

population, set first at 5 mSv and then at 1 mSv per year, has for decades been of the same order of magnitude as that due to natural irradiation. In contrast, progress should be particularly marked in knowledge of individual susceptibility to toxic agents in general and radiation in particular.

The challenge of radiotoxicology and nuclear toxicology will have been met if in the next few years physicians, research biologists and engineers succeed in formalising a consistent sum of knowledge concerning the hazards of radionuclides and non-radioactive substances used in all the applications of nuclear energy. One of the objectives currently being pursued is to take separate account of natural radiation, medical irradiation and environmental irradiation. But how can ever more complex knowledge be reconciled with the practical simplicity sought in radioprotection? "Elegant" means of prevention and treatment seem today to be a more accessible aim.

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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.

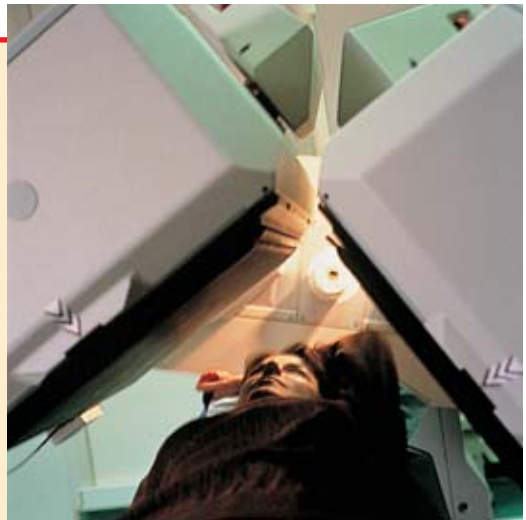
In the **Chernobyl accident** (Ukraine), which occurred in 1986, the total radioactivity dispersed into the atmosphere was of the order of 12 milliard milliard (10^{18}) becquerels over a period of 10 days. Three categories of radionuclides were disseminated. The first consisted of volatile fission products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

G The regulatory dose limits

Individual protection against the dangers of ionising radiation is based on two principles: (i) making sure a given radiation source irradiates exposed persons as little as possible (principle of optimisation), and (ii) making sure the exposure of a given individual remains below a certain level irrespective of the radiation source (principle of the dose limit).

These two principles are set out in the ICRP 60 recommendation published in November 1990(1) by the International Commission on Radiological Protection, the internationally recognised reference in the domain, and taken up in the Euratom 96/29 European directive of May 13 1996. The provisions of this directive were transposed into French law by the order of March 28 2001, the decree of March 8 2001 (modifying that of June 20 1966) and the decree of March 31 2003, which modify the public health and work codes accordingly.

Expressed in sieverts (Sv), the limits are of two sorts, global and local. Global limits are expressed in values of effective dose (Box F). It represents the acceptable risk level concerning the carcinogenic effect of ionising radiation. It is 20 mSv in 12 months for workers(2) in the nuclear field (in the broad sense) and 1 mSv per year for the general public. For a certain number of tissues and organs (skin, hands and feet, eye lens), a local limit is set with reference to deterministic risks of ionising radiation, namely radiodermatitis and cataract. This dose equivalent is thus set at 500 mSv for the skin and for the hands and feet, and 150 mSv for the eye lens. These values are ten times lower for the general public. These limits are for exposure resulting from human activities other than medical exposure(3).

Gonin/CEA

Dosicard dosimeter for real-time dosimetric monitoring.

Gonin/CEA

Passing through a detector frame for individual contamination at the exit from a controlled area – here the Osiris reactor at CEA Saclay Centre – is a regulatory obligation.

The effective dose takes into account both external exposure and internal exposure.

For internal exposure, there are tables setting limits for each radionuclide, mode of exposure (inhalation-ingestion) and age, taking into account their ranging "transferability" in biological media, and the dose per unit intake (DPUI) coefficients expressed in sieverts per becquerel (Sv / Bq), the becquerel being the unit of activity.

They indicate the internal dose that is "committed" for 50 years in adults and up to age 70 for children, taking into account the effective half life of the radionuclide in question. Because of children's greater susceptibility to radiation and the possibility of longer exposure for radionuclides with long effective half lives, the most restrictive annual intake limits are for infants aged up to one year, and the least restrictive for adults from age 17 as prescribed in the ICRP 67 publication of 1993.

The "inhalation" and "ingestion" DPUI values take respectively into account the new values of digestive absorption and the latest lung model(4) of the ICRP.

From these regulatory limits, radioprotection experts can calculate "derived" limits of levels in air or on surfaces, for example, for internal exposure hazards.

(1) Superseding ICRP 26 published in 1977.

(2) Persons directly assigned to work with ionising radiation in industry, research and medicine.

(3) The treatment of hyperthyroidism by irradiation, for example, involves an organ delivered dose of 70,000 mSv!

(4) Publication ICRP 66 of 1994 on the modelling of the human respiratory tract for radiological protection, which supersedes the lung model of ICRP 30.