The primary reason for comparing radiological and chemical hazards is, in the absence of knowledge of similarities between underlying mechanisms, the comparability of the methods used to evaluate their long-term consequences, especially at low doses: carcinogenicity, mutagenicity and effects on reproduction. For radiations, the evaluation is performed above all in terms of *risk quantification* while for chemicals *hazard identification* is the main concern.

Limits of the comparison between radiological and chemical hazards

Deterministic effects: safety is achievable

For both radiological and chemical hazards, it is today feasible to prevent most of the "**deterministic**" health disorders which occur beyond exposure thresholds, whether the **exposure** is acute (acute **irradiation** syndrome, lead encephalopathy, etc.) or chronic (pulmonary **fibrosis**, cadmium nephritis, berylliosis, etc.). *Exposure limit values* can be proposed when *thresholds* are determined and safety factors allowing for individual sensitivities are applied. This type of hazard control is straightforward except for some cases such for cadmium, for which there is still a dispute about the adverse potential of infra-clinical disturbances of renal function in populations contaminated by low levels of environmental cadmium

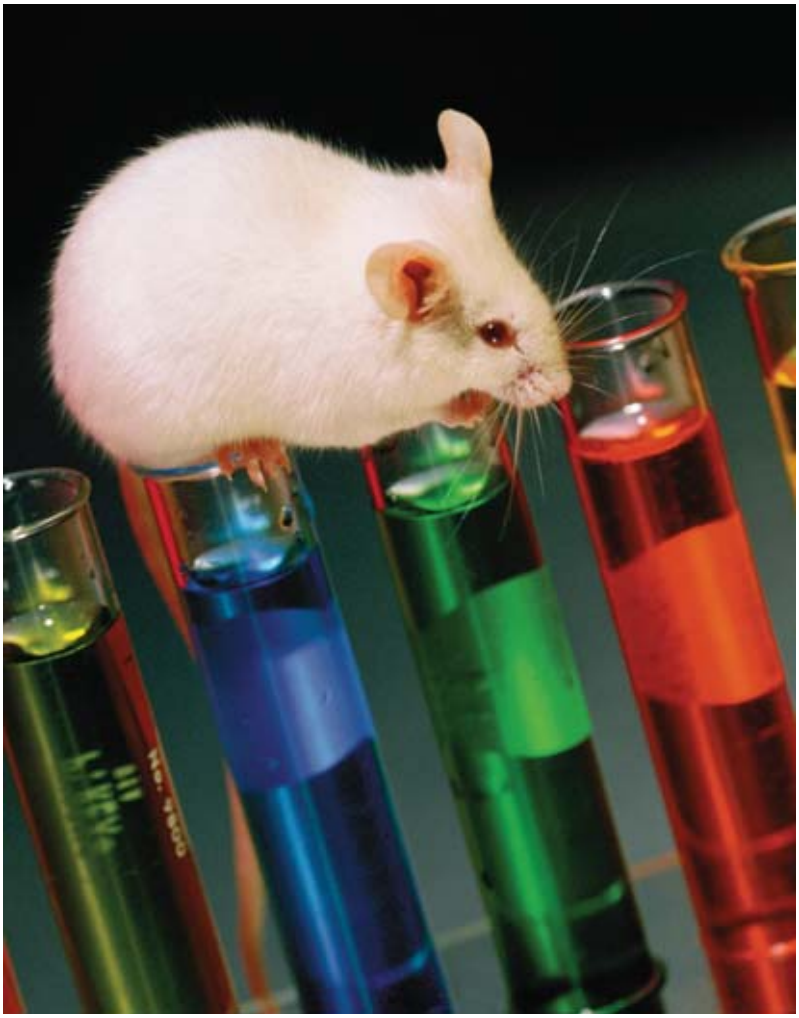
Differences in the evaluation of non-deterministic effects

Because they require the most stringent safety precautions, **carcinogenic** and **mutagenic** hazards and those linked to reproductive toxicity are of major concern for both **ionising radiation** and chemicals (e.g., metals). However, the evaluation is different for ionising radiations, for which *risk quantification* is predominating and for chemicals, for which *hazard identification* (Box 1) is the major concern, while risk assessment is generally approached semi-quantitatively.

The carcinogenic risk

Cancer hazard in man can be only identified by **epidemiology**. However, such an epidemiological evidence is generally difficult to interpret because of the long latency period, the non-specific nature (many possible causes) and the generally low incidence of the carcinogenic effect. Although a wide range of data demonstrate the carcinogenic effect of high **doses** for ionising radiations, there is practically no epidemiological evidence supporting carcinogenic effects in man for metals. The reasons are the very limited data on exposure most of which are generally mixed and very poorly assessed at the individual level. An exception is in the case of the nickel industry, for which an excess of lung and nose cancers was attributed to sulphur or oxide nickel species(1), and possibly to nickel soluble compounds.

(1) The best documented and directly comparable with ionising radiation, because there is no assumption of complex detoxification or activation metabolism.



Comstock

The laboratory rat is used for the assessment of both chemical and radiological risk. How validly the results of animal experimentation can be transposed to humans depends on the case.

1 The classification of hazardous substances

In Europe[1], the criteria for the regulatory classification of substances that are **carcinogenic, mutagenic** (hereditary genetic defects) or toxic to reproduction (fertility, pre- and postnatal development) are set by directive 67/548/EEC: the different categories defined for each of these effects are designed to rank the *estimated human risk* according to the quality of the available **epidemiological** and experimental data (results in animals and other relevant information):

Category 1: The evidence is sufficient to indicate a cause-effect relation in man.

Category 2: The evidence is sufficient to justify acting as if there is a cause-effect relation in man.

Category 3: The available evidence justifies concern but does not permit a satisfactory assessment.

The marketing or import for public sale of carcinogens in Categories 1 and 2, mutagens in Categories 1 and 2, and substances toxic to reproduction Categories 1 and 2, is forbidden.

(1) The classification systems of the WHO or the US EPA differ slightly.

Another source of uncertainty is the fact that exposures are in most cases combined. For example the contribution of arsenic cannot be discarded in the epidemiological studies on cadmium, in which the workers were assigned to broad exposure groups according to their jobs because of the lack of records on individual exposures. Practically all the metals recognised as carcinogenic in man were found to be so in heavily exposed workers in the past. Such exposure levels are today dramatically reduced, so that "historical" data are inappropriate for assessing the current risks. Furthermore, numerous factors (tobacco consumption, dietary habits, etc.) are not taken into account in the estimation of occupational cancer rates.

There is a large evidence that compounds shown to be carcinogenic in man are also carcinogenic in animals. It was therefore reasonable to assume that agents found to be carcinogenic in animals might be carcinogenic in man, even though there is no scientific method for quantitatively extrapolating to man data obtained from animal experiments, which are therefore only *qualitatively* predictive. The limits of the animal model are its variable statistical quality, the existence of specific **metabolisms** or pathological disorders with no human counterpart, the non-relevance of exposure routes, and very high spontaneous disease rates in some animals...

While recent experiments generally comply with "good laboratory practice", most animal studies on metals are not easy to interpret, because of the non-standardized exposure protocols and follow-up. Practically no study is of sufficiently high quality to rule out a cancer risk. There are many sources of bias: the cancers of the endocrine glands, of the liver, of the kidney or of the brain, for example, are dependent of changes in diet, and survival rate may be related to the reduction of the food consumption. Ignoring such factors can lead to consider as demonstrated an excess cancer which is only related to ageing. But the major bias is undoubtedly the observation of effects at dose levels close to the *maximum tolerated dose* (MTD), i.e., a dose for which the equilibrium of the cell dynamics is damaged and then cancers can occur through a simple increase of compensatory cell proliferation, in particular in the organs in which the spontaneous tumour rate is non-negligible. Apart from **genotoxic** compounds, substances usually have no *intrinsic* capacity to cause cancer. Their action depends heavily on conditions of administration, and this makes difficult to evaluate the carcinogenic potential in man under realistic conditions of exposure.

The cases of lead, cadmium and beryllium

The carcinogenicity of lead, cadmium and beryllium was recognised essentially from animal experiments (see *Beryllium, an example of a non-radioactive nuclear toxic element*).

Various questions subsist concerning the exposures routes, the observation of an excess of cancers beyond the *maximum tolerated dose* and the considerable differences that can occur between exposure and "dose". These parameters are of particular importance when the carcinogenic effect is limited to the lung: in rats, experimental coniotic[2] overload can be the unique cause of cancer linked to irritation resulting from the overwhelmed clearance[3] efficiency, and is observed for very low concentrations (a few microgrammes of beryllium).

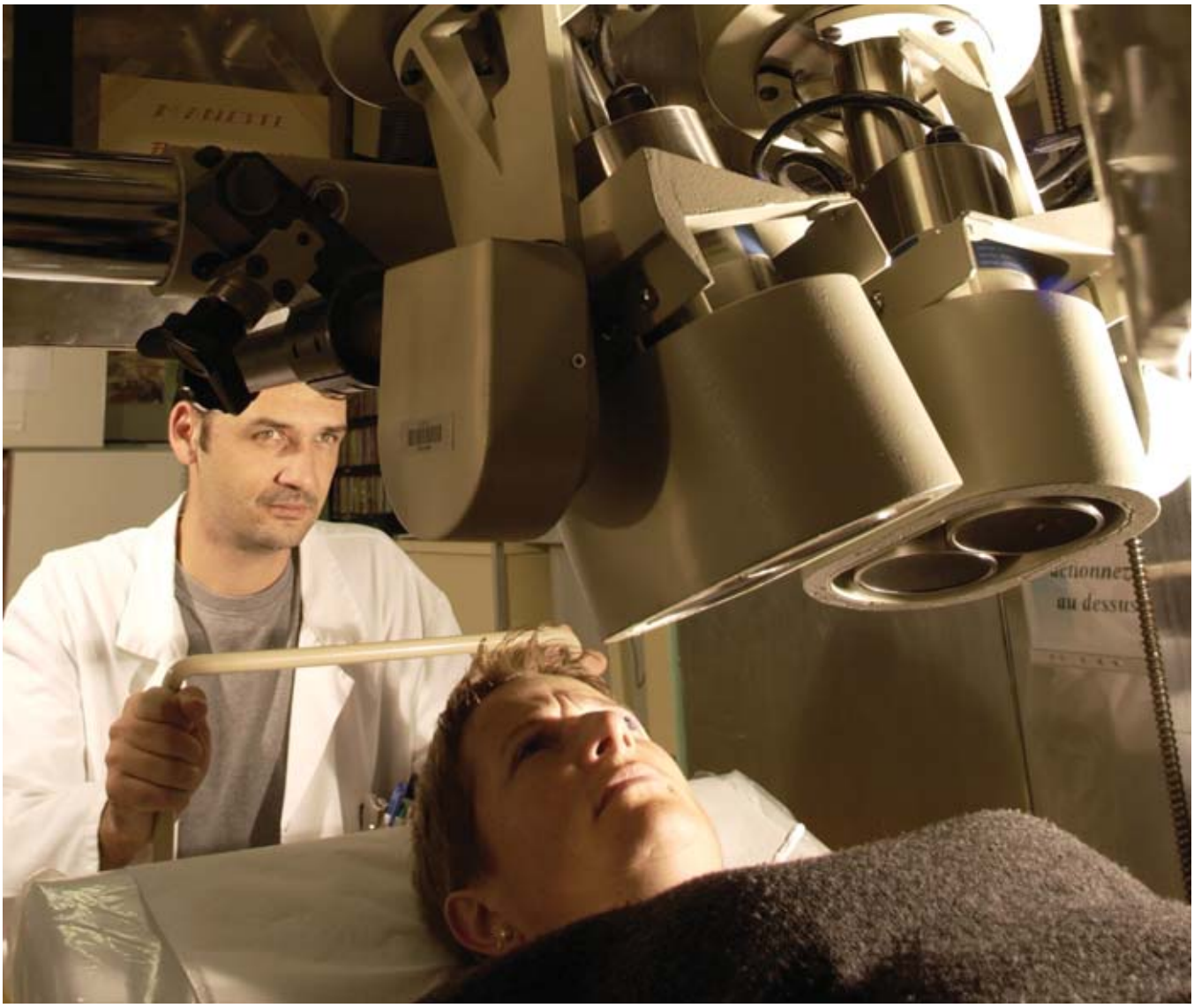
Carcinogens acting by the **ingestion** route are mostly systemic, i.e., prone to exert effects in remote organs, distant from the penetration or the deposition sites. It is then possible to establish a relation between their concentrations or those of their derivatives in biological fluids, and the incidence of cancer induced in the tissues. In addition, when the cancer occurs only at the administration site and when a contact carcinogenic effect is demonstrated, no causal relationship with the concentration of the carcinogenic agent in the human environment can be proposed.

The example of cadmium is a good illustration: this metal has only a very limited carcinogenic activity by ingestion, but it is an extremely efficient contact carcinogen at low dose, causing a **sarcoma** at the site of injection. It also induces an excess of **carcinoma** of the testicle after injection because it is **cytotoxic** for the seminiferous tubule. When inhaled, cadmium induces lung cancer in the rat at a concentration in air ten times lower than that tolerated for workers, making it one of the most powerful experimental pulmonary carcinogens known, while no excess cancers is observed in remote organ and tissues whatever the exposure level.

As occupational epidemiology is unable to demonstrate an excess of lung cancer in relation with cadmium exposure levels, is it possible to extrapolate rat data to man, knowing that negative epidemiological data do not prove that there is no risk? To what extent are rat and human lung tumours comparable? (see *Radon and lung cancer*). What is the magnitude of interspecies differences? This problem arises because lung carcinogenesis induced

(2) Coniosis: disease due to dust inhalation.

(3) Clearance: ability of a tissue or organ to eliminate a substance from an organic fluid.



Francis Vigouroux/CEA

Examination in the gamma counting unit of the occupation health service at the CEA Cadarache Centre (Bouches-du-Rhône). Occupational medicine provides data that radiobiology and nuclear toxicology, based on the most advanced biotechnology, link more and more closely to elementary biological mechanisms.

exclusively by **inhalation** is a particular case of contact carcinogenesis. Until now, only the rat exhibited lung cancers after cadmium exposure by inhalation, but not the hamster nor the mouse. Furthermore, differences in the carcinogenic induction pattern have been found for the various cadmium compounds. Then, either the carcinogenic effect is limited to the rat, or, more likely, the **speciation** of the compound at the site of its biological targets is subject to wide variations of toxicokinetic origin (deposition, uptake by target cells, binding to transport **proteins** masking the metal from its targets, etc…).

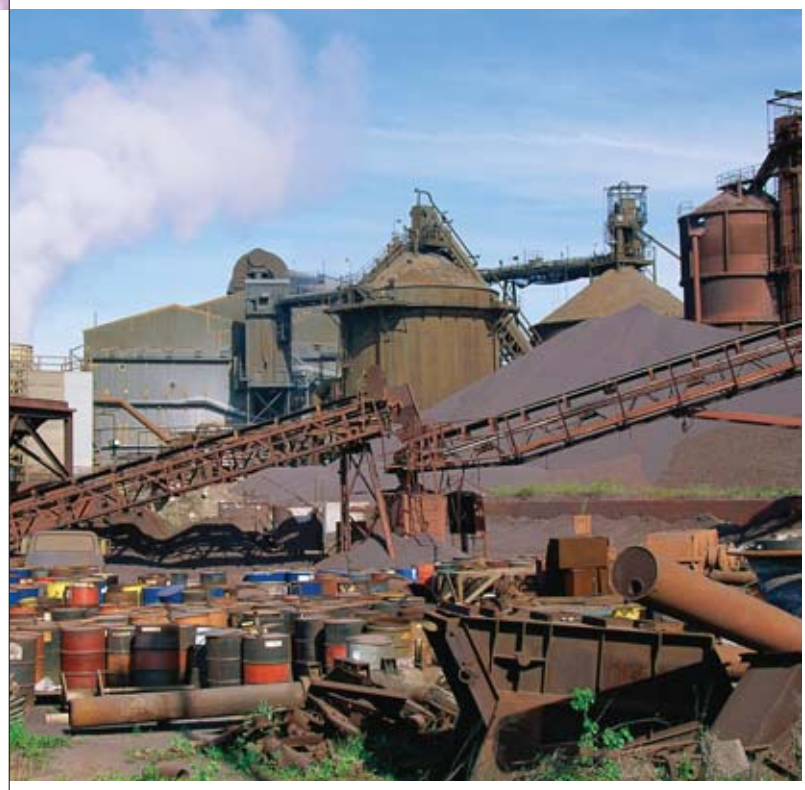
The difference in overall sensitivity to broncho-pulmonary cancer between rats and humans is difficult to appraise. The toxicokinetics of the inhaled carcinogen combine inextricably with tissue sensitivity to produce different exposure-effect relationships among mammalian species. An indirect approach is to compare the response among the two species to a physical genotoxic carcinogen such as ionising radiations, which operate independently of the metabolism and distribute homogeneously throughout the lung volume. In such a model, the overall sensitivity of the rat is obviously 4 to 5 times greater than that of man for a comparable number of **DNA** lesions.

Then, for a carcinogen such as cadmium, which needs no metabolic activation, of induction of cancer rates may be very markedly different in rats and in man.

The absence of carcinogenic effect in the mouse is difficult to explain by a large difference in induction sensitivity. It is seems therefore likely that a determining factor related to **bioavailability** in the target tissues has to be taken into account when results are to be extrapolated to man. This is a matter of expert decision-making, even though the identification of an intrinsic hazard is usually distinguished from the evaluation of the health risk.

Speciation of the cancer risk from chemicals

A generic classification ("metal and compounds") is applied by agencies when epidemiological evidence is inconclusive. This is supported by the classification of the **IARC** (International Agency for



PhotoDisc

Storage of materials on an old industrial site. Practically all the metals recognised as carcinogenic in man were identified in heavily exposed workers in the past.

Research on Cancer): the term "chemical agents" indicates pure substances, but also groups of substances or industrial processes. The evaluation of the carcinogenicity of compounds is thus based on the appraisal of experimental data the quality of which is not proportional to their number. The innumerable experiments on nickel inorganic compounds are demonstrative: the characterisation of physicochemical forms is generally imprecise, many studies include deficiencies precluding any conclusion about carcinogenicity. Data on relevant routes, in particular inhalation, are paradoxically scarce. Generally, animal experiments do not demonstrate any carcinogenic effect of nickel compounds following oral administration and the results for inhalation route are not conclusive(4). On the other hand, a local and sometimes significant carcinogenic effect had been demonstrated for most of the compounds following administration by non-relevant routes, but a systemic carcinogenicity is never observed. It must thus be concluded that high concentrations of nickel compounds are carcinogenic at the site of administration, particularly in mesenchymal(5) cells, which are very different from the **epithelial** target cells for lung cancer.

Different institutional viewpoints

The scientific evidence is often inadequate and results are conflicting. The absence consensus for setting safe levels of exposure results in large differences in controlling practices. This is evidenced by the lack of any standard definition of carcinogenesis. For the IARC, carcinogenesis is the induction of unusual tumours and (or) an excess rate of common tumours (despite fundamental differences in mechanisms). For the American Occupational Safety and Health Administration (**OSHA**), a *potential occupational carcinogen is* any substance, or combination or mixture of substances responsible for an increase in the **incidence** of benign or malignant tumours, or for a marked shortening or tumour latency, in man or in one or more animal species after oral, respiratory, dermal or other exposure route inducing tumours at sites other than the site of administration. The EEC relies only on substances inducing cancers or increasing their incidence after ingestion, inhalation or dermal exposure.

The toxic risk for reproduction

The classification of toxicity for reproduction relates to a broad range of effects from libido to perinatal development. Regulations specify three levels of investigation: fertility (in both sexes), development and lactation. This class of metal toxicity lends itself well to regulation of exposure, including by inhalation, because it shows effects at often very low levels owing to the sensitivity of the fetus and **germinal** tissue, and the multiplicity of mechanisms that can be involved during organ formation and growth. It also enables authorities to propose threshold levels below which no effect is expected. In general, this cannot be done for carcinogens, or, by their very nature, for **mutagens**. However, there is a risk of abuse of this category because of the non-specific consequences induced by the level of exposure corresponding to the maternal MTD. The detection of an occupational teratogen(6) is generally difficult, except in the case of an extremely toxic substance producing a high percentage of specific malformations at a certain period (e.g., mercury in Minamata disease).

The mutation risk

Mutagenic substances, which can transmit hereditary genetic alterations, are classified into three groups by the European regulations. No **heavy metal** has

(4) With the exception of excess lung cancer in the rat exposed to nickel subsulphide.

(5) Mesenchyme: immature non-specialised form of conjunctive tissue.

(6) Teratogenic: able to induce malformations.

Risk and safety factors in toxicology 2

In the usual approach to toxicology acceptable **exposure** thresholds are set by applying a safety factor to the lowest dose for which no harmful effect has been observed in the most sensitive species (most sensitive effect in most sensitive species). This safety factor has one or more components:
A factor of 10 to allow for extrapolation between species.
A factor of 10 to allow for extrapolation within species (individual susceptibility).
A factor of 2 to 10 to allow for uncertainties in data, type of effect, etc.
Mutagens (and **mutagenic carcinogens**) are generally excluded from the system (no-threshold assumption not recognised).

yet been included in Category 1 proven human **mutagens**. Although metals, in particular mercury, cadmium, nickel and chromium definitely induce genotoxic effects (on mitosis, unscheduled DNA synthesis, sister chromatids exchange, interaction with heterochromatin(7), induction of single strand breaks)(8), there is to date no evidence that these effects are associated with the appearance of stable transmissible **mutations**.

As relatively few substances have been identified as carcinogens in man, and as most carcinogenic substances also exert mutagenic effects, short-term mutagenesis tests have been developed. The transmission of *somatic* cell mutations (to be separated from mutations of *germinal* cells, which are transmissible to progeny) is considered as a key mechanism in the carcinogenic process. Simple and cheap ***in vitro*** or ***in vivo*** tests are especially useful, noteworthy because labelling a substance as mutagenic is as restrictive as labelling it as carcinogenic, and the classification is based exclusively on experimentation.

Toxicity evidenced by epidemiology, the basis of regulation

Most of the agencies involved in identifying of chemical hazards do not propose any risk estimate (Box 2), one of the reasons for this is probably related to the difficulties in defining acceptable exposure levels. In this respect, metals raise an obvious question: some definitely produce experimental carcinogenic effects; chromium, nickel and arsenic are directly implicated, through certain industrial processes, in the induction of human cancers. Others, such as iron, cadmium, lead and beryllium are suspected, in the absence of any epidemiological consensus, although various agencies have already decided to list them among proven carcinogens, at least by inhalation.

In practice, animal experiments are the only source of quantified data from which regulations can propose to manage risk. Consequently, close attention should be made less on the most sensitive protocol but more on the relationship between cancer-inducing potential and toxicokinetics. The reasonable way is probably totake into account epidemiological evidence of toxicity in the conditions of lowest exposure (nephro-toxicity of cadmium, immu-notoxicity of beryllium, neurotoxicity of lead, etc.). The data obtained from the study of the reproductive and developmental pathology induced by metals can also form an efficient basis for regulation, insofar as the embryo, neonate and infant, and the germinal tissues, generally prove especially vulnerable to intoxication by metals.

Attempts at more direct comparison

Many attempts to compare radiological and chemical risks "*in typical conditions of exposure throughout working life*" have been made, but results are disappointing. Reviewing more 5,000 references on some hundred substances for which a human effect had been reported, a study by the American NRC (Nuclear Regulatory Commission) pointed out the deficiency in *quantitative* data on chemical substances. One of the alternatives proposed to allow a "more direct" comparison between chemical and radiological risk, was to calculate the loss of life expectancy, which gives comparable results for the risk of cancer among nuclear workers, estimated by **linear no-threshold** extrapolation of the effects of ionising radiation, and the risk among workers in major industries (nickel refining or manufacture of glass fibre, mineral wool and plastics) estimated from epidemiological data.

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(7) Heterochromatin: region of a **chromosome** that remains inactive between two cell divisions.

(8) On this subject, see *Clefs CEA* No. 43 (spring 2000).

Beryllium, an example of a non-radioactive nuclear toxic element

A long known toxicity

Beryllium is a good example of a non-nuclear toxic element long used in nuclear research and industrial applications for its thermal and mechanical properties, and its nuclear behaviour as a neutron moderator and reflector. It is also used in sectors such as the aerospace industry and in radiology.
This radiostable chemical **element** is a lung toxic with delayed effects that may appear up to thirty years after **exposure**. The average regulatory exposure level is currently quite low: 2 µg/m³. Measures of protection against exposure to beryllium dust were taken as soon as it began to be used.
At CEA, strict safety precautions for its use were prescribed in the early sixties. Beryllium was handled at Fontenay-aux-Roses (Hauts-de-Seine) in airtight glove boxes or under a ventilated hood(1). It was also used in laboratories in Saclay (Essonne) and for military applications at Vaujours (Seine-et-Marne). The toxicity of the metal was thus recognised by CEA from the very start, as regards means of protection and *a posteriori* analysis and measures.

Biokinetics

The main entry route of beryllium is **inhalation** of dust and **aerosols**. Absorption in the lungs is the main hazard. Beryllium binds to plasma **proteins** and is transported in the body, where its accumulates in the liver, bones, kidneys and **lymph ganglia**. However, its distribution and excretion vary according to the physicochemical properties of the compound inhaled. Inhaled beryllium metal is more toxic than inhaled oxide. Beryllium is weakly absorbed in the gastro-intestinal tract (formation of insoluble phosphates, which are eliminated).
Entry by the cutaneous route is also minor and occurs only through damaged skin. Elimination, chiefly in the urine, can continue to take place long after exposure. Its **biological half life** is long: twenty years after exposure, traces of beryllium can still be found in urine. As levels in urine are very low, usually less than 2 µg/l, specific analytical methods had to be developed, using, for example, atomic absorption spectrometry or mass spectrometry.

Particularly toxic soluble forms

Beryllium and its compounds are toxic, especially certain soluble forms (fluoride or sulphate). The dose-response curve is not linear and displays variations. From the results of skin tests, the nature of granulomatous lesions and the response to treatment with corticoids, the hypothesis of an immuno-allergic mechanism is currently favoured, but no specific antigen(2) has been found.
The antigen response requires an association with a protein or other macromolecule. Elevated gamma-globulin levels and **lymphocytal** reactions noted in chronic beryllium disease thus support an immuno-allergic response. The lymphoblast trans-formation test can be used to detect sensitivity to beryllium.
The **carcinogenic** effect of this metal has been demonstrated experimentally and beryllium is considered as a potential human carcinogen. Berylliosis is officially recognised as an occupational illness.

Health disorders linked to beryllium

Acute effects

Acute or subacute **intoxication** by inhalation injures the upper airways (e.g., causing rhinopharyngitis), the conjunctiva (tears), and the lungs (broncho-pneumopathy with cough and hindered breathing, sometimes accompanied by signs of general illness such as fever and tiredness). There is a risk of lung cancer. Radiological imaging shows diffuse **fibrosis** and (or) a micro-nodular appearance.
Cutaneous penetration can occur *via* sites of integumental damage. After an irritation phase, an allergic reaction appears, sometimes with ulceration. Subsequent evolution towards a subcutaneous *granuloma* (inflammatory tumour) can take place after several months.

Chronic diseases

Chronic berylliosis can appear 5, 10, or even 30 years after exposure, sometimes with few symptoms and only radiological anomalies or functional signs (cough, breathing difficulties), accompanied by general signs (tiredness, weight loss, etc.). Adverse effects on the heart, kidney stones with elevated urine calcium have been reported. Radiologically, the image of fibrosis evolves towards opacities and inflammatory nodules. In more severe forms the respiratory symptoms are emphasised. An enlarged spleen and liver and arthropathy can be found, together with increased blood cell volume relative to whole blood volume, and elevated **serum** proteins (gammaglobulins).
The obstructive respiratory syndrome requires the prescription of corticotherapy.
In very severe forms, cases of spontaneous *pneumo-thorax* (the abnormal presence of air in the pleural cavity) have been described, and evolution towards cachexia is possible.
Medical follow-up consists essentially of monitoring blood parameters, urine assays and respiratory function (functional and radiological exploration).

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CEA Headquarters (Paris)

(1) A report by the Radiation Protection Service in 1963 states the regulations applicable to the handling of beryllium and its compounds. Notes from the High Commissioner for Atomic Energy in 1982 and 1987 state the rules of protection for the handling of beryllium and its compounds.

(2) Antigen: a molecule able to bring about an immune response by induction of antibodies.

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.

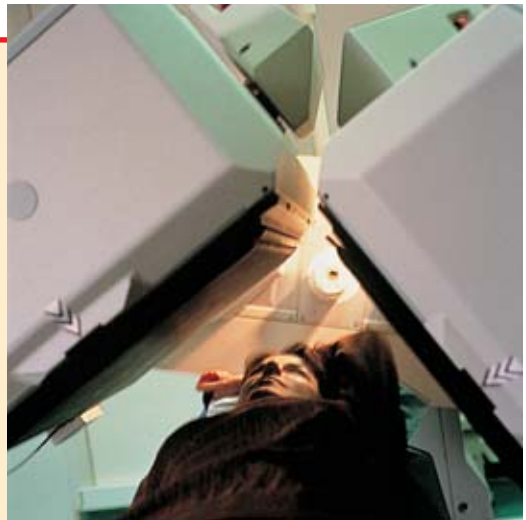
In the **Chernobyl accident** (Ukraine), which occurred in 1986, the total radioactivity dispersed into the atmosphere was of the order of 12 milliard milliard (10^{18}) becquerels over a period of 10 days. Three categories of radionuclides were disseminated. The first consisted of volatile fission products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